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Contents

Page

Systemic Lupus Erythematosus after "Idiopathic" Thrombocytopenic Purpura: A Review. A Study of Systemic Lupus Erythematosus Occurring after 78 Splenectomies for "Idiopathic" Thrombocytopenic Purpura, with a Review of the Pertinent Literature. YALE RABINOWITZ and WILLIAM DAMESHEK 1

Absorption of Radioactive B_{12} in Patients with Pernicious Anemia after Long-Term Oral and Parenteral Therapy. P. J. FOUTS, O. M. HELMER and S. M. CHERNISH 29

Renal Patterns in Myeloma. L. M. SANCHEZ and C. A. DOMZ 44

Diabetic Acidosis: An Evaluation of the Cause, Course and Therapy of 73 Cases. ALAN S. COHEN, VERNON K. VANCE, JOHN W. RUNYAN, JR. and DAVID HURWITZ 55

Combined Primary and Secondary Hyperparathyroidism: Two Case Reports and a Review. EMANUEL GOLDBERG and RICHARD M. TORACK 87

Studies of Cholinesterase Activity. V. Serum Cholinesterase in Patients with Carcinoma. HOWARD J. WESTSTONE, RUDOLPH V. LAMOTTA, ALDO BELLUCCI, ROBERT TENNANT and BENJAMIN V. WHITE 102

Peculiar Familial and Malignant Pheochromocytomas of the Organs of Zuckerkandl. J. E. COOK, R. W. URICH, H. G. SAMPLE, JR. and N. W. FAWCETT 126

The Normal Systolic Murmur. DALE GROOM, WADDY CHAPMAN, WOFFORD W. FRANCIS, ANNE BASS and YRO T. SILVONEN 134

Phonocardiography in Pulmonary Stenosis: Special Correlation between Hemodynamics and Phonocardiographic Findings. E. GREY DIMOND and ALBERTO BENCHIMOL 145

The Effect of Childbearing on the Course of Rheumatic Heart Disease: A 25-Year Study. EDWIN P. MAYNARD, JR. and VICTOR GROVER 163

Manual Compression of the Carotid Vessels, Carotid Sinus Hypersensitivity and Carotid Artery Occlusions. ALLEN SILVERSTEIN, DAVID DONIGER and MORRIS B. BENDER 172

The Status of Tranquilizing Drugs—1959. BENJAMIN BOSHES 182

Analgesic Effect of Dextropropoxyphene Hydrochloride in Elderly Patients with Chronic Pain Syndromes. R. W. BOYLE, C. E. SOLOMONSON and J. R. PETERSEN 195

Combined Clinic:

The Lymphomas: Combined Clinic at the College of Physicians and Surgeons, Columbia University, New York, N. Y. 201

Case Reports:

Nocardiosis of the Central Nervous System: Report of Two Fatal Cases. CLAUDE M. CURP, WALTON M. EDWARDS and EDWARD A. CLEVE 223

Xanthomatous Biliary Cirrhosis Secondary to Carcinoma of the Extrahepatic Bile Ducts. LEONARD J. STUTMAN and RICHARD C. BOZIAN 229

Tracheopathia Osteoplastica. JOHN S. SHUTTLEWORTH, CAMERON L. SELF and HUGH S. PERSHING 234

Chronic Neutropenia in Siblings: The Effect of Steroids. PHILLIP L. ROSSMAN and GEORGE J. HUMMER 242

Fatal Miliary Coccidioidomycosis Complicating Prolonged Prednisone Therapy in a Patient with Myelofibrosis. JOHN J. CASTELLOT, ROBERT L. CREVELING and FORREST W. PITTS 254

Typhoid Fever Complicated by Intestinal Perforation and Myocarditis. JOHN D. WOFFORD, CLINTON E. WALLACE and FRED ALLISON, JR. 259

Editorials—The Bulletin of the American College of Physicians 268

The Present Status of Peripheral Arterial Reconstruction for Arteriosclerosis Obliterans 268

Reviews 273

Medical News i

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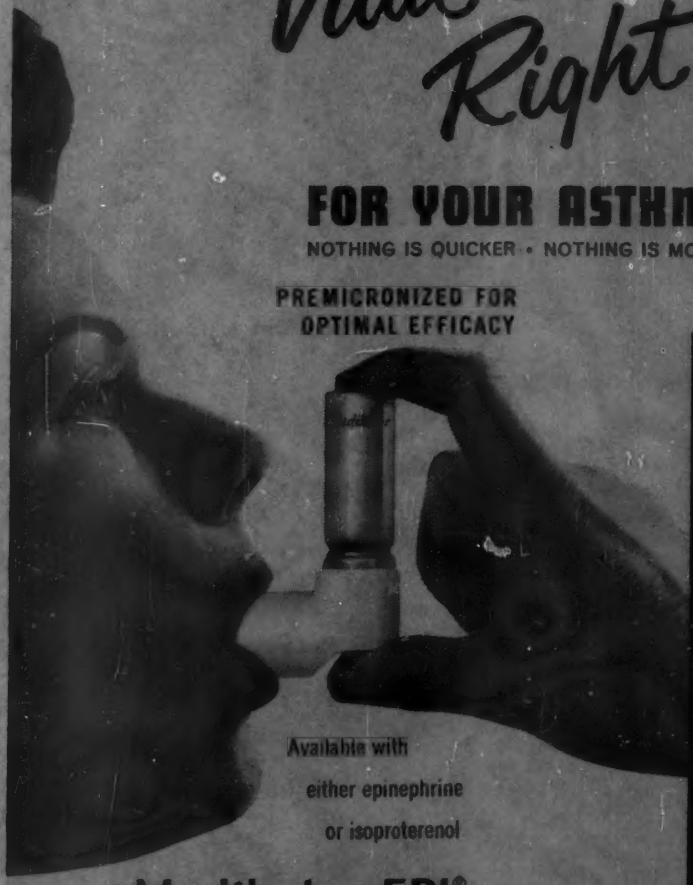

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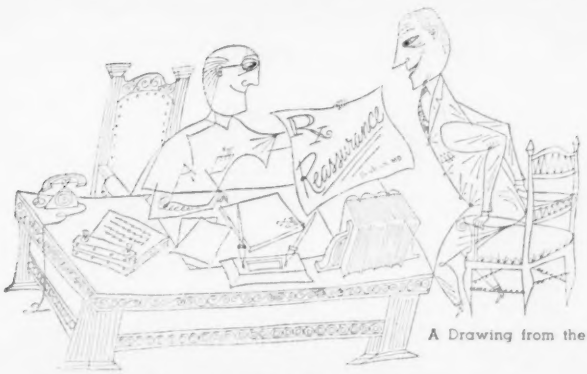

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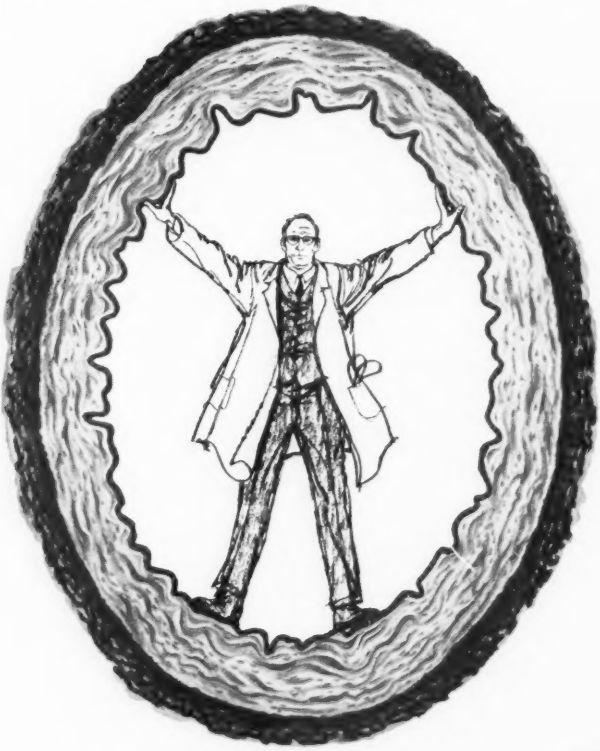

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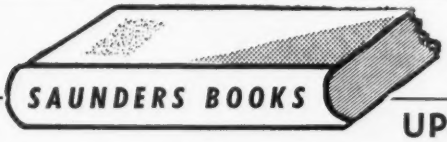

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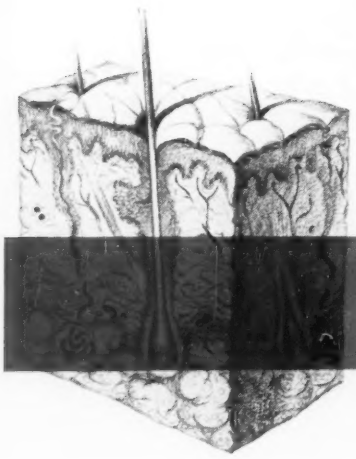

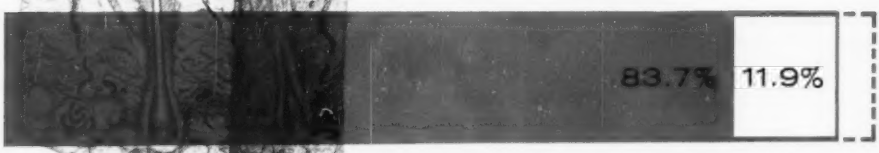

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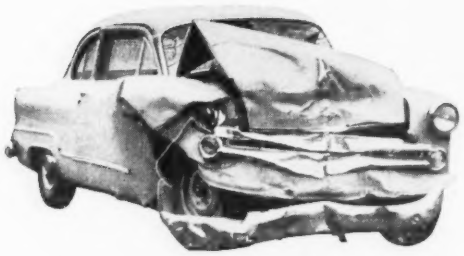

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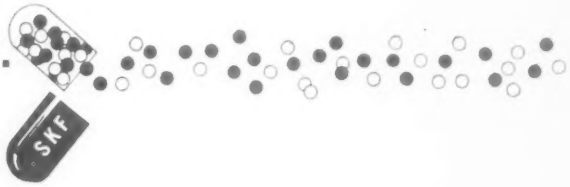

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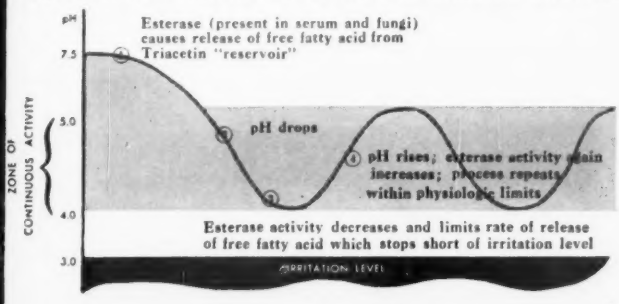
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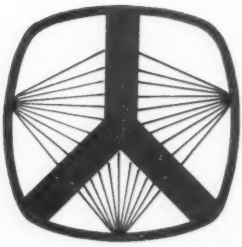

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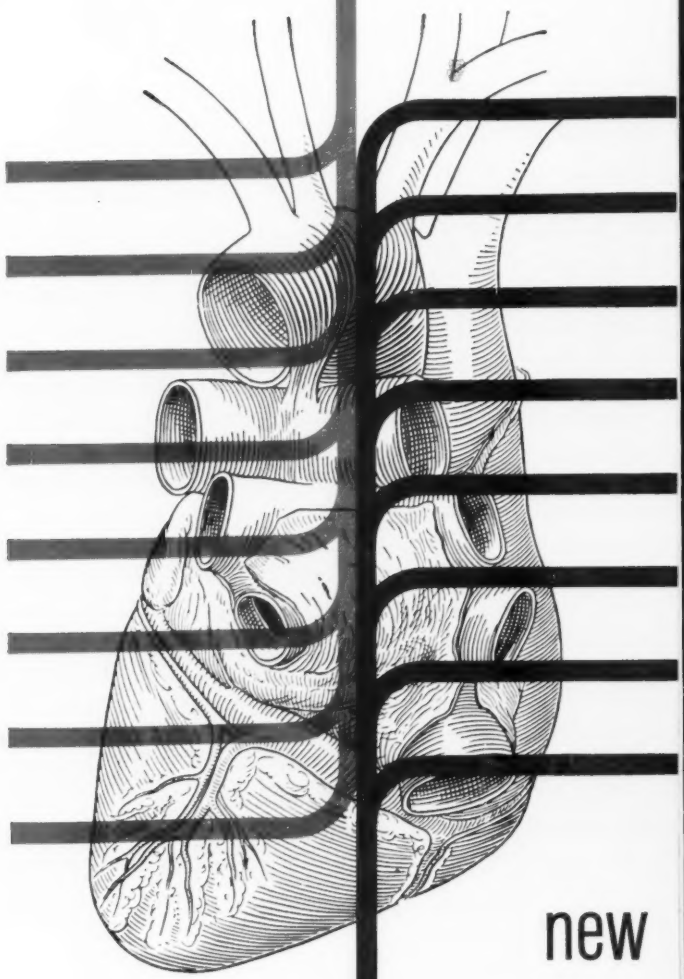
Available in easy-to-swallow Filmtabs® (100 and 250 mg.); in tasty, citrus-flavored Oral Suspension (200 mg. per 5-ml. teaspoonful).

ABBOTT

FILMTABS—FILM-SEALED TABLETS, ABBOTT. 001189

new approach to the concept of "total management" in angina pectoris



new

Marplan prevents or reduces anginal pain — Marplan, a new, safer and therapeutically more effective amine oxidase inhibitor, produced "excellent effects with relatively small doses"[1] when used on a continuing dosage schedule in patients with angina pectoris. Indicated primarily for patients with moderately severe to intractable angina pectoris, Marplan often "afforded greater relief than any other compound. . . ."[1] Response to Marplan is usually seen in a reduction of the number and severity of attacks, with consequent lowering of nitroglycerin requirements.

A recent Marplan report from the literature[2]

Patients	*Age*	*Diagnosis*	*Usual Dose*	*Duration of Treatment*
31	40's-70's	Angina pectoris. "About one-half were severely ill."	15-30 mg/day	1-9 mos.

Results: "Over 70 per cent of the patients reported notable benefits. . . ."[2]

Marplan creates a more confident mental climate — The profound antidepressive action of Marplan also controls the components of anxiety and hopelessness, which so often aggravate angina pectoris. Patients display a "more cheerful outlook,"[1] improving the chances of success of the entire prophylactic regimen.

Marplan strikes a happy balance of potency/safety — Marplan has been tested longer, and in more patients, than any of the recently introduced amine oxidase inhibitors. There have been no reports of liver damage attributable to Marplan or any other serious toxicity. Nevertheless, all precautions set forth in the product literature should be strictly observed. Specifically, since the precise manner in which Marplan improves the cardiac status is as yet undefined and since so many patients attain a virtually pain-free state, it is imperative that patients be instructed to maintain the same restrictions of activity in force prior to Marplan therapy.

Supplied: 10-mg tablets in bottles of 100 and 1000.

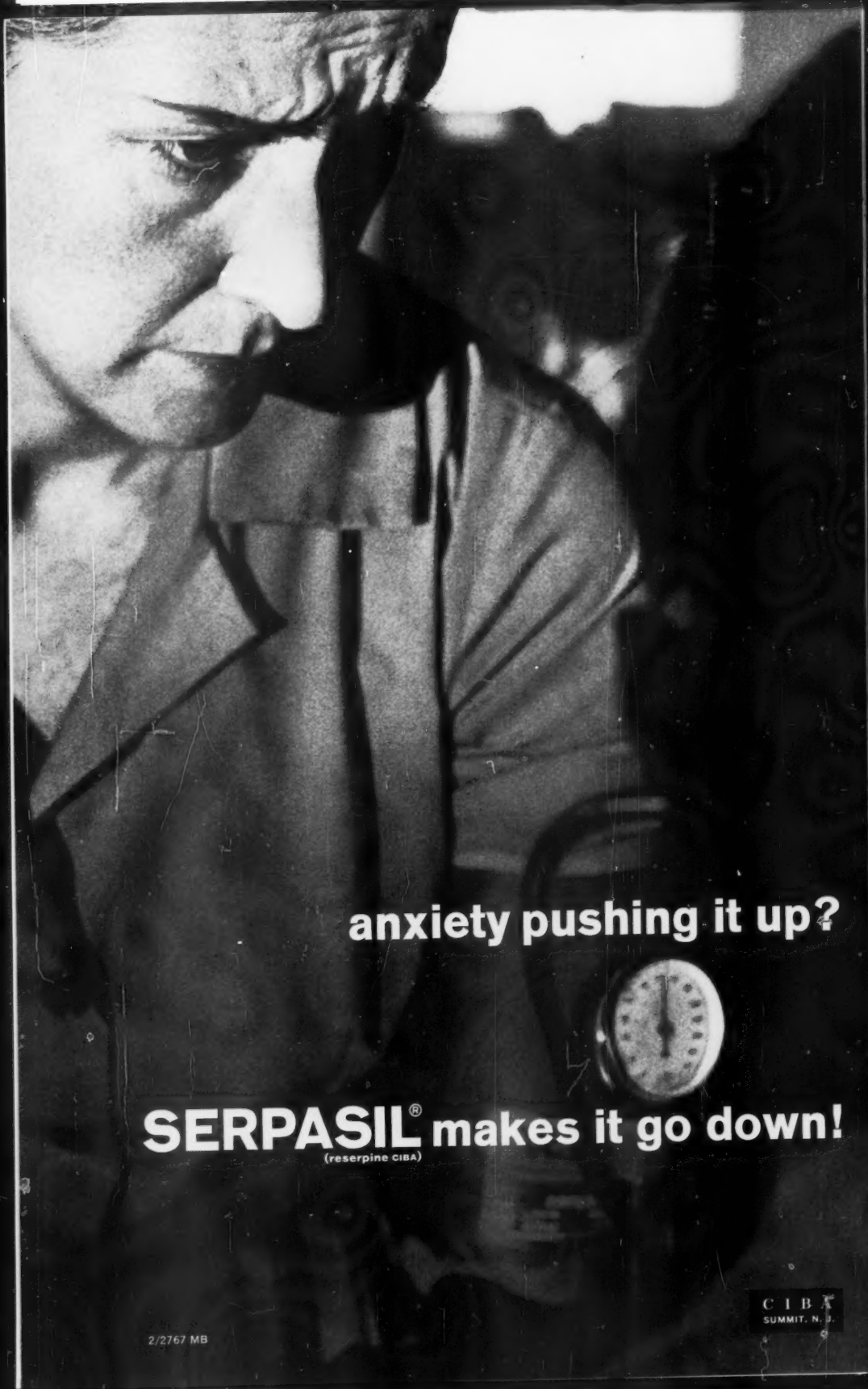
References: 1. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 2. G. C. Griffith, *Clin. Med.*, 6:1555, 1959.

MARPLAN™—1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine
ROCHE®

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc • Nutley 10 • N. J.

Marplan

a happy balance of potency/safety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SERPASIL®
(reserpine CIBA)
makes it go down!
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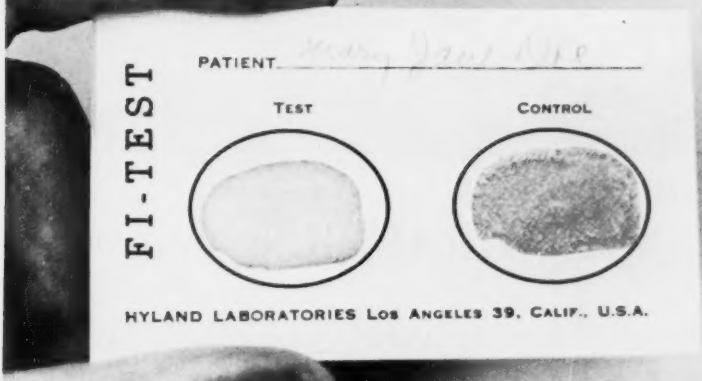
RAPID SCREENING TEST FOR

HYPOFIBRINOGENEMIA



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Test results at patient's bedside – from skin puncture to reading – in less than 2 minutes. Only one drop of blood required. Test performed by simple, rapid-slide technic.

FI-TEST indicates whether fibrinogen content is above or below 100 mg-%, the concentration considered critical. Easy-to-read results indicate promptly whether or not replacement fibrinogen is needed. (If reading shows a normal fibrinogen level, needless replacement therapy may be avoided and the physician is alerted to seek another explanation for continued bleeding.)

Supplied in compact ready-to-use kits containing complete materials for 6 determinations.

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160 Lockwood Ave., Yonkers, N.Y.

SYMPOSIUM REPORT:

ALTAFUR in antibiotic-resistant staphylococcal infections

ALTAFUR proved superior to any other single agent against staphylococcal infections encountered in the pediatric section of a general hospital. Introduced during an epidemic of severe staphylococcal pneumonia and bronchiolitis in younger children, ALTAFUR was employed in treating a total of 59 infants or juvenile patients, most of whom had upper or lower respiratory tract involvement. Almost all had been given antibiotics without effect; 34 were judged severely or critically ill. Cures were obtained in 54 of these patients after a 3 to 10 day course of ALTAFUR. There was only one failure (results were inconclusive in the remaining four cases). Mixed infections with Pneumococcus or Streptococcus sp. also responded readily.

ALTAFUR was administered orally in varying dosage: the optimal dose is believed to be about 22 mg./Kg. daily.

Side effects were minimal in these patients, being limited to gastric intolerance in a few cases, usually controllable by giving the drug with or after meals. Laboratory studies performed before and after ALTAFUR treatment revealed no adverse influence on renal, hepatic or hematopoietic function, nor other signs of toxicity.

In vitro, staphylococci isolated in this series proved uniformly susceptible to ALTAFUR, whereas many strains were resistant to a variety of antibotics. With ALTAFUR as with all nitrofurans, the lack of development of significant bacterial resistance is considered a major advantage over other antimicrobials.

Lysaught, J. N., and Cleaver, W.: Paper presented at the Symposium on Antibacterial Therapy, Michigan and Wayne County Academies of General Practice, Detroit, Sept. 12, 1959 (published Nov., 1959)

bright new star

in the antibacterial firmament

ALTAFUR™

brand of furaltadone

the first nitrofuran effective orally in systemic bacterial infections

- Antimicrobial range encompasses the majority of common infections seen in everyday office practice and in the hospital
- Decisive bactericidal action against staphylococci, streptococci, pneumococci, coliforms
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- Development of significant bacterial resistance has not been encountered
- Low order of side effects
- Does not destroy normal intestinal flora nor encourage monilial overgrowth (little or no fecal excretion)

Tablets of 50 mg. (pediatric) and 250 mg. (adult)
Average adult dose: 250 mg. four times a day, with food or milk
Pediatric dosage: 22-25 mg./Kg. (10-11.5 mg./lb. body weight daily in 4 divided doses

CAUTION: The ingestion of alcohol in any form, medicinal or beverage, should be avoided during Altafur therapy.

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Just an hour of pitching baseball with my son and I "threw my arm out." Painful? I couldn't even sleep that night!

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I saw my doctor that night and got a prescription for some tablets.

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Salts of Dihydrohydroxycodeinone and Homatropine, plus APC

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FOR PAIN

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AND THE PAIN WENT AWAY FAST

ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients. **VERSATILE**—new "demi" strength permits dosage flexibility to meet each patient's specific needs. PERCODAN-DEMI provides the PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit-forming. Federal law permits oral prescription.

Each PERCODAN® Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. phenacetin, and 32 mg. caffeine.

*U.S. Pat. 2,626,185

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Literature? Write
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for the tense and nervous patient

relief comes fast and comfortably

–does not produce autonomic side reactions
–does not impair mental efficiency, motor control, or normal behavior.

Usual Dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets or as MEPROTABS*—400 mg. *unmarked,* coated tablets.

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meprobamate (Wallace)

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Traffic: jammed
Car: stalled
Temper: mild
Ulcer: quiet

Here's a man whose ulcer once would have protested strongly—not just at traffic problems—but at the entire gamut of stress to which modern man is subjected.

His physician, aware that *the patient as well as the ulcer* must be treated, has prescribed ALUDROX SA.

eases tension • promotes healing relieves pain • reduces acid secretion • inhibits gastric motility

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Suspension and Tablets: Aluminum Hydroxide Gel with Magnesium Hydroxide, Ambutonium Bromide and Butabarbital, Wyeth

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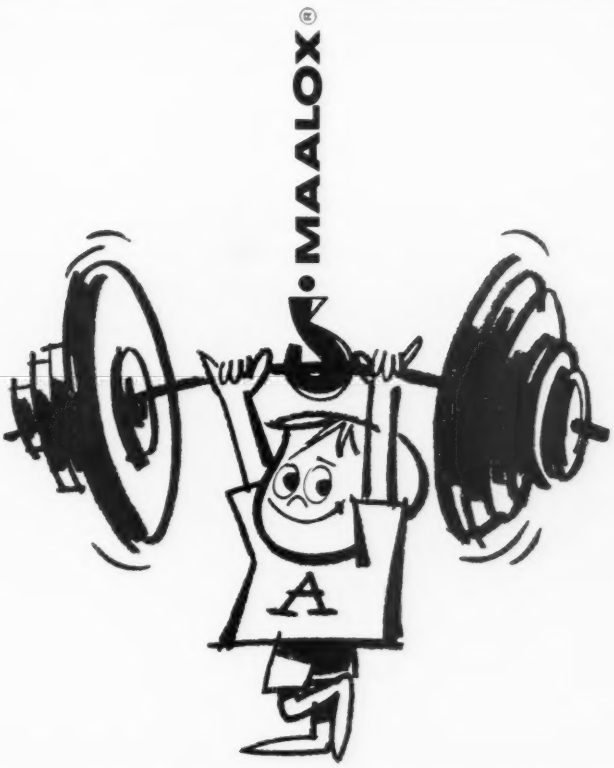

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ASCRIPTIN (RORER)

particularly suited for arthritic patients

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Mysteclin-V — specific action plus added protection. Mysteclin-V is a combination of tetracycline phosphate complex — one of the world's most widely prescribed broad spectrum antibiotics — and Mycostatin, the first well-tolerated antifungal antibiotic. Together, in Mysteclin-V, these two components provide specific, effective antibiotic action plus added protection against fungal superinfections.[1-3]

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References: 1. Cronk, G. A.; Naumann, D. E., and Casson, K.: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 397. 2. Childs, A. J.: Brit. M. J. *1*:660 (Mar. 24) 1956. 3. Newcomer, V. D.; Wright, E. T., and Sternberg, T. R.: Antibiotics Annual 1954-1955, New York, Medical Encyclopedia, Inc., 1955, p. 686.

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Each black and white capsule contains:
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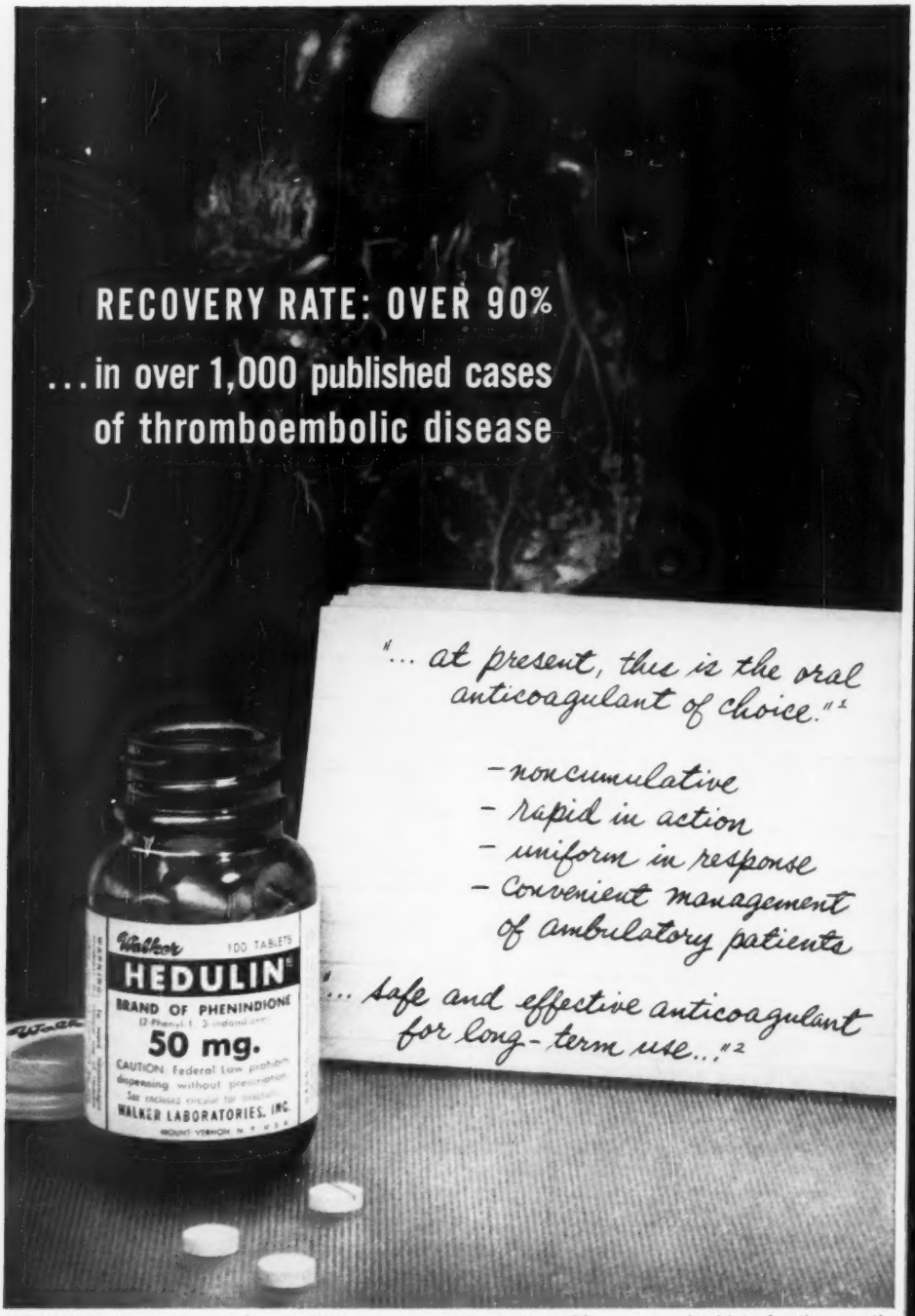
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- noncumulative
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100 TABLETS
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955. 2. Tandowsky, R. M.: Am. J. Cardiol. 3:551 (April) 1959.

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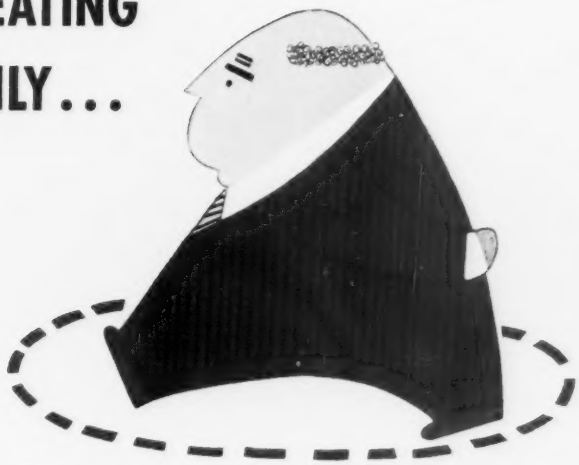

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sublingual ergotamine tartrate tablets

STOPS THE ATTACK WITH "PARENTERAL" SPEED AND SUBLINGUAL CONVENIENCE

■ faster than any oral tablet—faster than the time needed to obtain, prepare and give an injection, and get an effect. Tablets dissolve under the tongue within 30 seconds, effects start with the speed of circulation time, relief in the 90 per cent range is established within 10 to 15 minutes.

■ the tiny sublingual tablets can be placed under the tongue any time, anywhere—no need for water, privacy, or sterile precautions.

Supplied: Ergomar Sublingual Tablets,† 2 mg. ergotamine tartrate per tablet, in specially designed dispenser package of 12 tablets. For patient economy and convenience, we suggest prescribing 12 tablets.

†brand of specially processed ergotamine tartrate, patent pending

KEEPS MORE PATIENTS HEADACHE-FREE MORE EFFECTIVELY

NORDSON PHARMACEUTICAL LABORATORIES, INC. • Irvington, New Jersey

Check cough 8-12 hours

with a single dose

Rx TUSSIONEX®

A 'Strasionic' Antitussive • Dihydrocodeinone Resin—Phenyltoloxamine Resin

"STRASIONIC RELEASE" MAKES THE BIG DIFFERENCE

- Permits Natural Discharge of Mucus
- Predictable Antitussive Action
- Minimum Amount of Narcotic

TWO FORMS: Tussionex Thixaire™ Suspension • Tussionex Tablets

Each teaspoonful (5c.c.) or tablet provides 5 mg. dihydrocodeinone and 10 mg. phenyltoloxamine as resin complexes.

Dose: 1 teaspoonful or tablet q12h. Children under 1 year, ¼ teaspoonful q12h; 1-5 years, ½ teaspoonful q12h.

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Nicotinamide	50 mg.	11 ozs. of roasted peanuts
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Ascorbic acid (Vitamin C)	**250 mg.**	¾ lb. of cooked broccoli

*These common foods are among the richest sources of B vitamins and ascorbic acid. H. A. Wooster, Jr., Nutritional Data, 2nd Ed., Pittsburgh, 1954.

Allbee® with C

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A. H. ROBINS COMPANY, INC.
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the beauty of these antitussives:

hey help the cough remove its cause

These elegant antitussives comprise a group of significantly superior expectorants from which you may select the formula best suited for your coughing patient.

First of all, they have more in common than mere delectability to eye and palate: they all include *glyceryl guaiacolate*. This remarkable expectorant aids the coughing mechanism by increasing the secretion of Respiratory Tract Fluid,[1] which helps liquefy sputum,[1,3] makes bronchial and tracheal cilia more efficient,[1,2] and acts as a demulcent.[1,3-5] Through its effects, all four expectorants promote the natural purpose of the cough, which is to remove the irritants that cause it.[1,2]

In addition, the Robins antitussive armamentarium provides a choice of widely accepted drugs in various combinations with glyceryl guaiacolate for treating different kinds of coughs and associated symptoms. For antihistaminic effects, there is Dimetane® or prophenpyridamine; for bronchodilation and nasal decongestion, there are sympathomimetic agents; and for suppression of the "too frequent" cough, there is codeine or dihydrocodeinone.

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Each teaspoonful contains:
Glyceryl guaiacolate ..... 100 mg.

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Each teaspoonful contains:
Glyceryl guaiacolate ..... 100 mg.
Prophenpyridamine maleate ... 7.5 mg.
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(exempt narcotic)

Dimetane® Expectorant

Each teaspoonful contains:
Parabromdylamine maleate (DIMETANE) ..... 2 mg.
Glyceryl guaiacolate ..... 100 mg.
Phenylephrine HCl, USP ..... 5 mg.
Phenylpropanolamine HCl, NNR ..... 5 mg.

Dimetane® Expectorant-DC

Each teaspoonful contains the Dimetane Expectorant formula *plus* Dihydrocodeinone bitartrate, NF ..... 1.8 mg.
(exempt narcotic)

References: 1. Cass, L. J., and Frederik, W. S.: Am. Pract. & Digest Treat. *2*:844, 1951. 2. Blanchard, K., and Ford, R. A.: Journal-Lancet *74*:443, 1954. 3. Hayes, E. W., and Jacobs, L. S.: Dis. Chest *30*:441, 1956. 4. Blanchard, K., and Ford, R. A.: Rocky Mountain M. J., Vol. 52, No. 3, 1955. 5. Boyd, E. M., and Pearson: Am. J. M. Sc. *211*:602, 1946.

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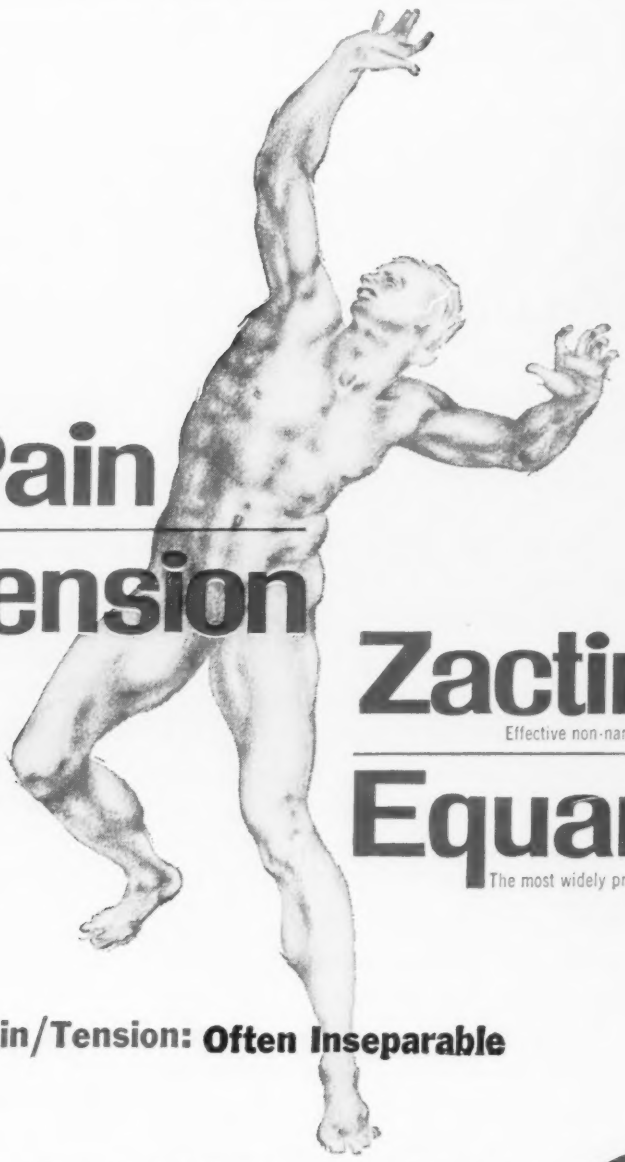

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Zactirin®*
Effective non-narcotic analgesia

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The most widely prescribed ataraxic

Pain/Tension: Often Inseparable

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EQUANIL enhances the action of ZACTIRIN by reducing the tension which often accompanies pain and increases awareness of it. *Wyeth Laboratories, Philadelphia 1, Pa.*

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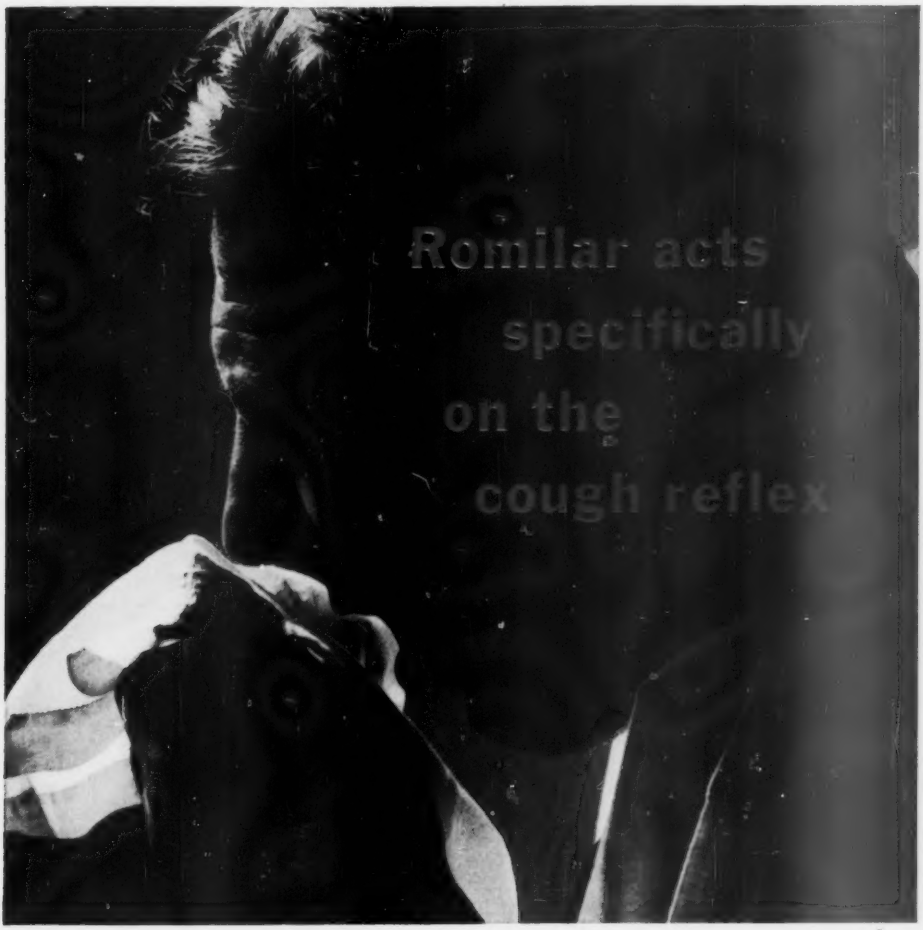

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ROMILAR, the non-narcotic cough specific, has one pharmacologic action—cough suppression. There is no central depressant or analgesic effect; and there is no tolerance liability, no addictive potential.[2-9]

Bibliography: (1) N. Ralph, Am. J. M. Sc. 227:297, 1954. (2) H. A. Bickerman, In W. Modell, Ed., Drugs of Choice 1958-1959, St. Louis, The C. V. Mosby Company, p. 557. (3) H. A. Bickerman, E. German, B. M. Cohen and S. Itkin, Am. J. M. Sc. 234:191, 1957. (4) L. J. Cass, W. S. Frederik and J. B. Andosca, Am. J. M. Sc. 227:291, 1954. (5) L. J. Cass and W. S. Frederik, J. Lab. & Clin. Med. 48:879, 1956. (6) L. J. Cass and W. S. Frederik, New England J. Med. 249:132, 1953. (7) H. Isbell and H. F. Fraser, J. Pharmacol. & Exper. Therap. 107:524, 1953. (8) W. M. Benson, P. L. Stefko and L. O. Randall, J. Pharmacol. & Exper. Therap. 109:189, 1953. (9) New and Nonofficial Drugs 1959, Philadelphia, J. B. Lippincott Company, p. 326.

Supply: ROMILAR Syrup in bottles of 4 oz, 16 oz and 1 gal. ROMILAR Tablets in bottles of 20, 100 and 500.
Romilar® Hydrobromide—brand of dextromethorphan hydrobromide.

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Produce remission or improvement in 70-85% of cases

Act effectively in all types of depression

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Achieve therapeutic benefit with minimal risk of serious side reaction

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The efficacy of Tofranil is attested by more than 50 published reports and confirmed by clinical experience in more than 50,000 cases.

Detailed Literature Available on Request.

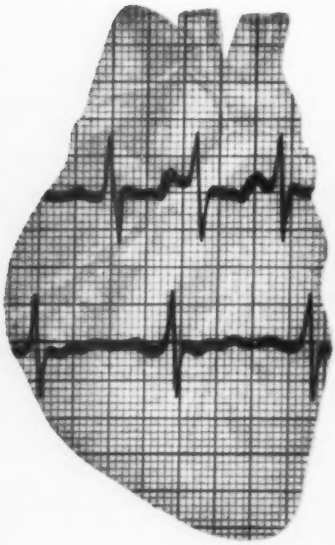
Geigy, Ardsley, New York

Geigy

13759

in atrial fibrillation

suitable for conversion



a "drug of choice is quinidine"[1]

QUINAGLUTE®
DURA-TAB S. M.

the only oral Sustained Medication* quinidine gluconate, 5 gr.

is a quinidine of choice[2]

in all CARDIAC ARRHYTHMIAS

premature contractions, auricular tachycardia, flutter, fibrillation

- **b.i.d. dosage** — each dose of Quinaglute Dura-Tab S.M. maintains uniform plasma levels up to 12 hours.
- no night dose needed.
- quinidine gluconate is more soluble, better absorbed and tolerated than quinidine sulfate.

Dosage: For **conversion** of auricular fibrillation to normal sinus rhythm, in most cases, 2 Quinaglute Dura-Tab S.M. tablets 3 to 4 times a day, for 2 to 3 days.

For **maintenance** 1 to 2 tablets every 10 to 12 hours.

Supplied: Bottles of 30, 100 and 250.

samples, reprint and detailed literature.

1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

*U.S. PATENT 2,895,881

REFER TO PDR
PAGE 893

WYNN PHARMACAL CORPORATION
5119 West Stiles Street, Philadelphia 31, Pa.

new for total management of itching,[1,2] inflamed,[3,4] infected[5,6] skin lesions

Dermatitis repens [with staph and monilia] 7 weeks duration

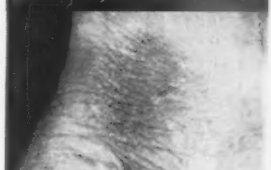
Cleared in 5 days

Mycolog ointment

Kenalog, Spectrocin and Mycostatin in Plastibase

antipruritic/anti-inflammatory/antibacterial/antifungal

Infectious eczematoid dermatitis of ankle—5 years duration



Cleared in 20 days

Mycolog Ointment – containing the new superior topical corticoid Kenalog – reduces inflammation,[3,4] relieves itching,[1,2] and combats or prevents bacterial, monilial and mixed infections.[5-7] It is extremely well tolerated, and assures a rapid, decisive clinical response for most infected dermatoses.

> "Thirty-one of 38 patients . . . obtained excellent or good control of dermatological lesions . . . [Mycolog] was highly effective, particularly in the management of mixed infections. Several recalcitrant eruptions which had not responded to previous therapy were remarkably responsive to the daily application of this preparation over periods of 2 to 3 weeks."[8]

For total management of itching, inflamed, infected skin lesions, Mycolog contains triamcinolone acetonide, an outstanding new topical corticoid for prompt, effective relief of itching, burning and inflammation[1-4] – neomycin and gramicidin for powerful antibacterial action[7] – and nystatin for treating or preventing Candida (Monilia) albicans infections.[8,9]

Application: Apply 2 to 3 times daily. Supply: 5 Gm. and 15 Gm. tubes. Each gram supplies 1.0 mg. (0.1%) triamcinolone acetonide, 2.5 mg. neomycin base, 0.25 mg. gramicidin, and 100,000 units nystatin in PLASTIBASE.

References: 1. Shelmire, J.B., Jr.: Monographs on Therapy 3:164 (Nov.) 1958. • 2. Nix, T.E., Jr., and Derbes, V.J.: Monographs on Therapy 3:123 (Nov.) 1958. • 3. Robinson, R.C.V.: Bull. School of Med., U. Maryland 43:54 (July) 1958. • 4. Sternberg, T.H.; Newcomer, V.D., and Reisner, R.M.: Monographs on Therapy 3:115 (Nov.) 1958. • 5. Clark, R.F., and Hallett, J.J.: Monographs on Therapy, 3:153 (Nov.) 1958. • 6. Smith J.G., Jr., Zawisza, R.J., and Blank, H.: Monographs on Therapy, 3:111 (Nov.) 1958. • 7. Monographs on Therapy, 3:137 (Nov.) 1958. • 8. Howell, C.M., Jr.: North Carolina M.J. 19:449 (Oct.) 1958. • 9. Bereston, E.S.: South. M.J. 50:547 (April) 1957.

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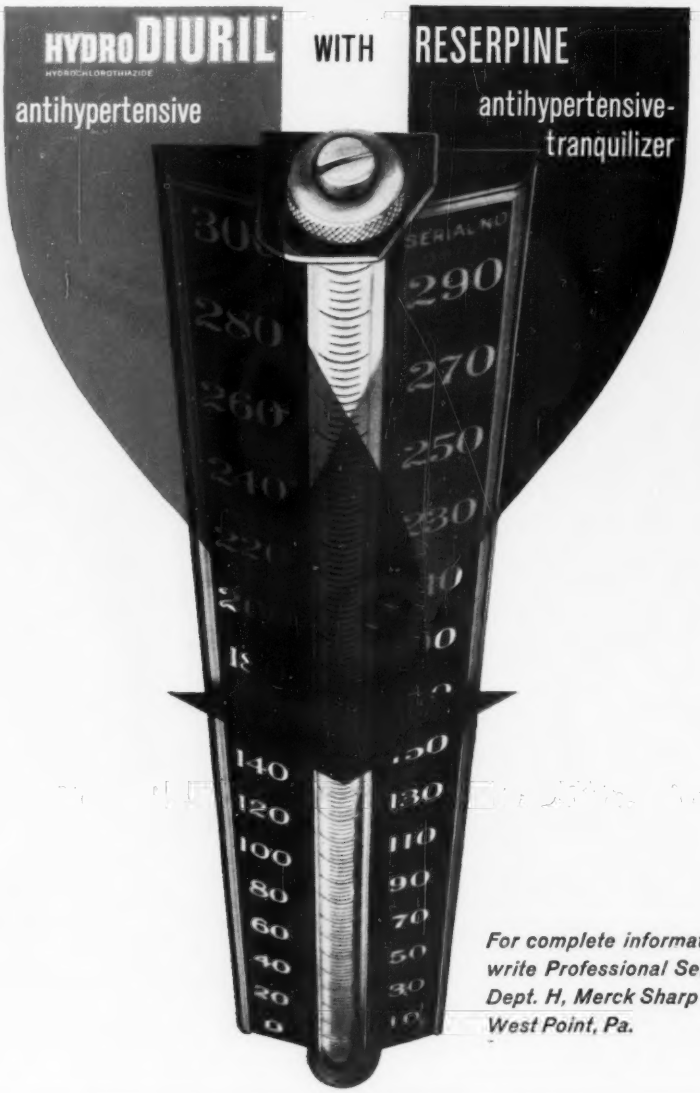

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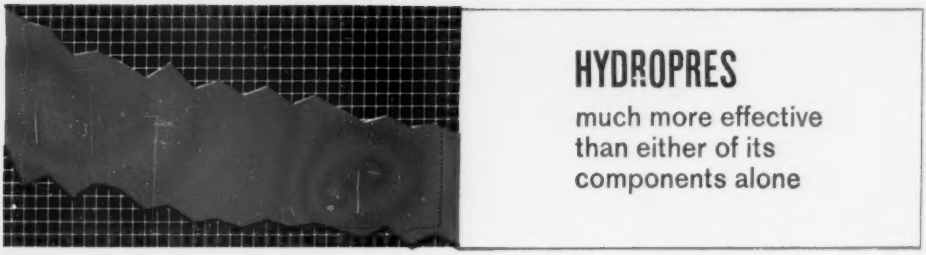

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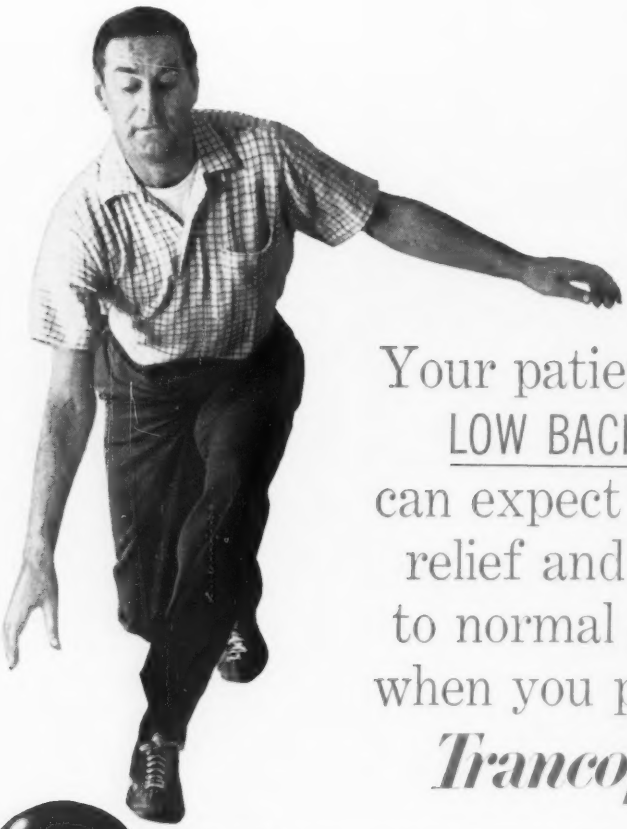

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can expect striking
relief and return
to normal activity
when you prescribe
Trancopal

case profile.[1] A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted. For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

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Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

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(1) Hootnick, H. L.: Jnl. Amer. Ger. Soc., 4:1021-1030, 1956. (2) Cass, L. J. and Frederik,W. S.: Jnl. Lancet, 73: 414-416, 1953. (3) Marshall,W.: So. Dak. J. Med. & Pharm. 8:151:153, 1955.

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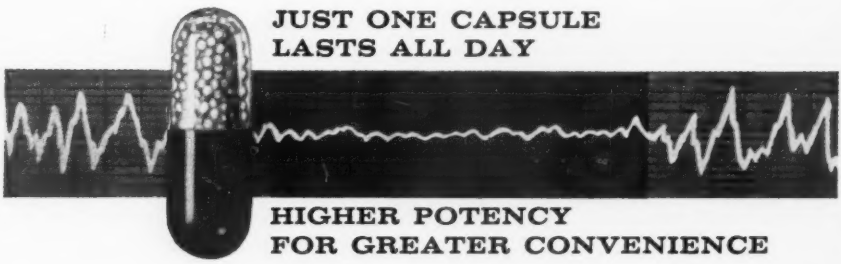

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1. Spies, T. D.: J. A. M. A. 167:675 (June 7) 1958.

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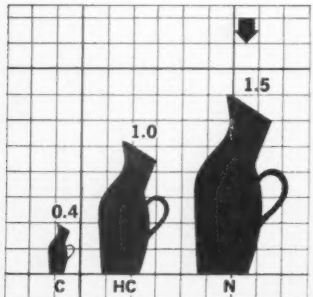
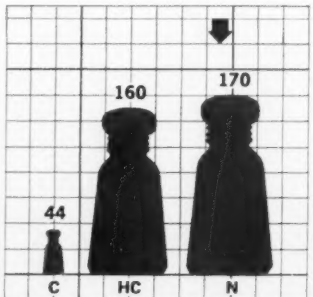
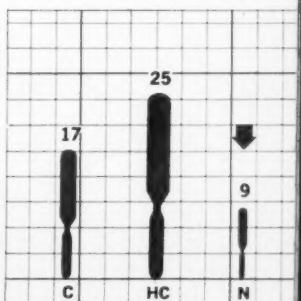
Comparison of electrolyte excretion pattern for the 24 hours followin typical doses of chlorothiazide, hydrochlorothiazide, and Naturetin



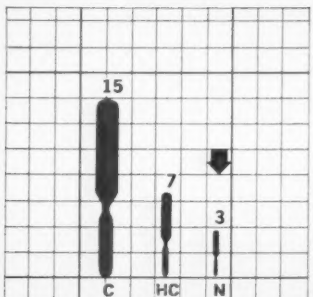
Urinary Volume (liters) significantly increased with Naturetin



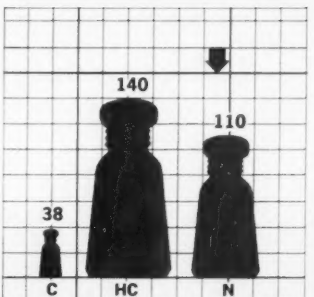
Natriuresis (mEq./24 hr.) sodium excretion significantly increased with Naturetin



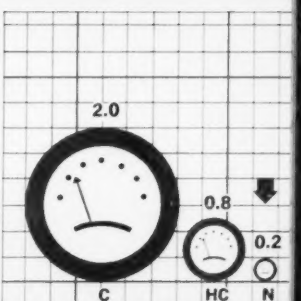
Potassium Excretion (mEq./24 hr.) least with Naturetin



Bicarbonate Excretion (mEq./24 hr.) least with Naturetin



Chloride Excretion (mEq./24 hr.) marked increases



Urinary pH least increase with Naturetin

Typical Doses: Chlorothiazide – 1,000 mg.; Hydrochlorothiazide – 50 mg.; Naturetin (Benzydroflumethiazide) – 5 mg.

1. Adapted from: Ford, R. V., Squibb Clin. Res. Notes 2:1 (Dec.) 195

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A single 5 mg. tablet once a day provides all these advantages[2]

- prolonged action – in excess of 18 hours
- convenient once-a-day dosage
- low daily dosage – more economical for the patient
- no significant alteration in normal electrolyte excretion pattern
- repetitively effective as a diuretic and antihypertensive
- greater potency mg. for mg.–more than 100 times as potent as chlorothiazide
- potency maintained with continued administration
- low toxicity – few side effects – low salt diets not necessary
- comparative studies with chlorothiazide, hydrochlorothiazide, and Naturetin disclose that smallest doses of Naturetin produce greater weight loss per day
- in hypertension, Naturetin, alone or in combination with other antihypertensives, produces significant decreases in mean blood pressure and other favorable clinical effects
- purpura and agranulocytosis not observed
- allergic reactions rarely observed

[2]Reports (1959) to the Squibb Institute for Medical Research.

Naturētin – *Indications:* in control of edema when diuresis is required, in congestive heart failure, in the premenstrual syndrome, nephrosis and nephritis, cirrhosis with ascites, edema induced by drugs (certain steroids); in the management of hypertension, used alone, combined with Raudixin (Squibb Rauwolfia Serpentina Whole Root), or with other antihypertensive drugs, such as ganglionic blocking agents.

Contraindications: none, except in complete renal shutdown.

Precautions: when Naturetin is added to an antihypertensive regimen including hydralazine, veratrum, and/or ganglionic blocking agents, immediate reduction must be made in the dosage for all preparations; the dosage for ganglionic blocking agents must be decreased by 50% to avoid a precipitous drop in blood pressure. This also applies if these hypotensive drugs are added to an established Naturetin regimen . . . in hypochloremic alkalosis with or without hypokalemia . . . in cirrhotic patients or those on digitalis therapy when reductions in serum potassium are noted . . . in diabetic patients or those predisposed to diabetes . . . when increased uric acid concentrations are noted . . . when signs–leg or abdominal cramps, pruritus, paresthesia, rash–suggestive of hypersensitivity, are noted.

Naturētin – *Dosage: in edema,* average dose, 5 mg., once daily, preferably in the morning; to initiate therapy, up to 20 mg., once daily or in divided doses; for maintenance, 2.5 to 5.0 mg., daily in a single dose. *In hypertension:* suggested initial dose, 5 to 20 mg. daily; for maintenance, 2.5 to 15 mg. daily, depending on the individual response of the patient. When Naturetin is added to an antihypertensive regimen with other agents, lower maintenance doses of each drug should be used.

Naturētin – *Supplied:* tablets of 2.5 mg. and 5 mg. (scored).

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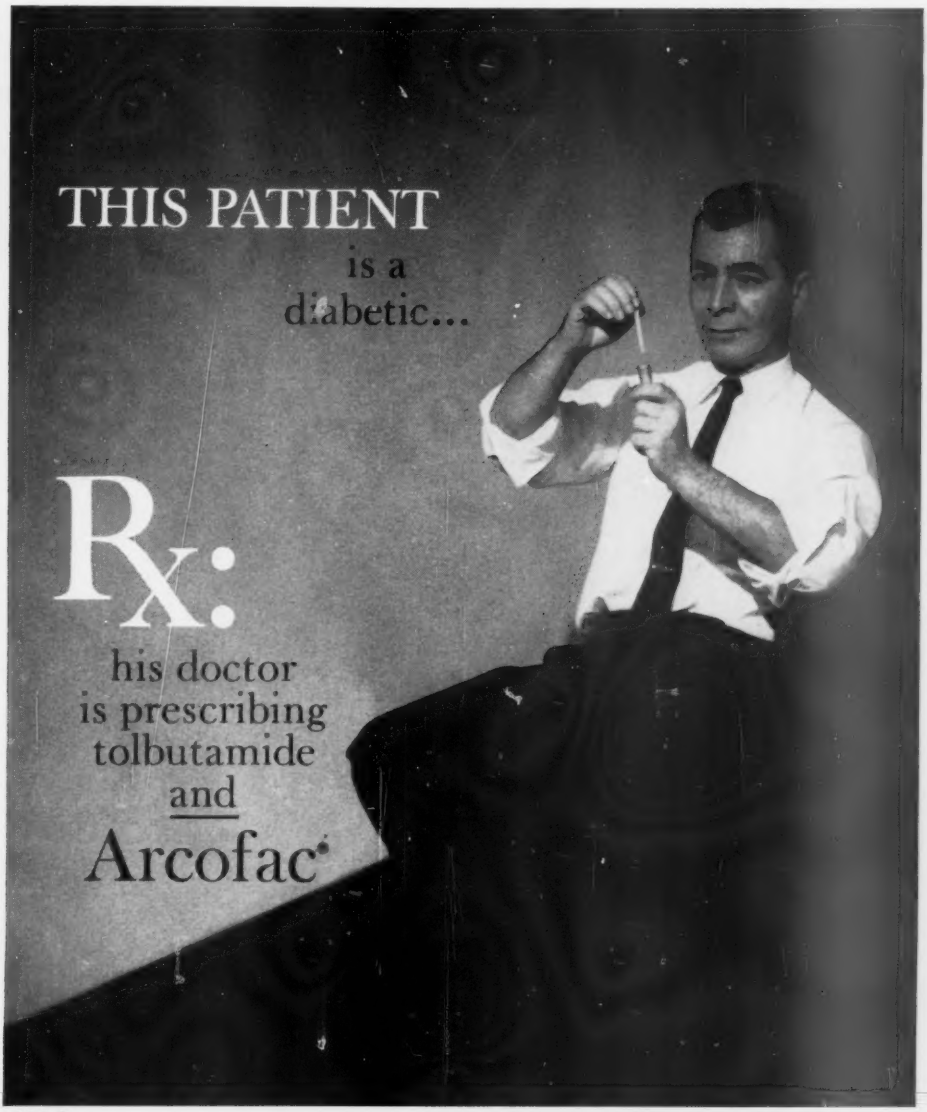

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1. Hufford, A. R.: Rev. of Gastroenterology 18:588.

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Formula: each tablet or 10 cc. gel contains—

Bentyl (dicyclomine) hydrochloride	5 mg.
Aluminum hydroxide gel	400 mg.
Magnesium oxide	200 mg.
Methylcellulose	100 mg.
Sodium lauryl sulfate	25 mg.

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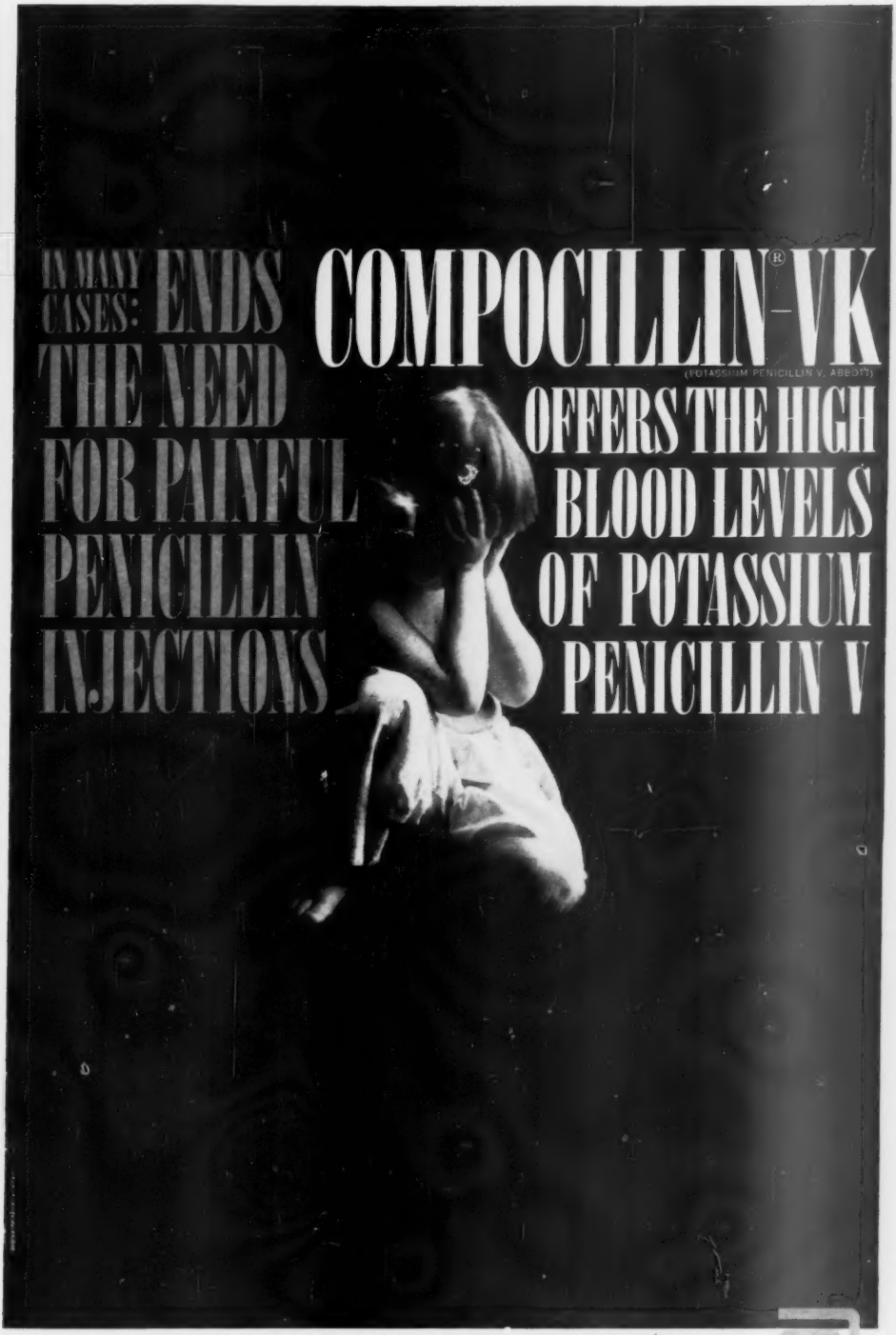
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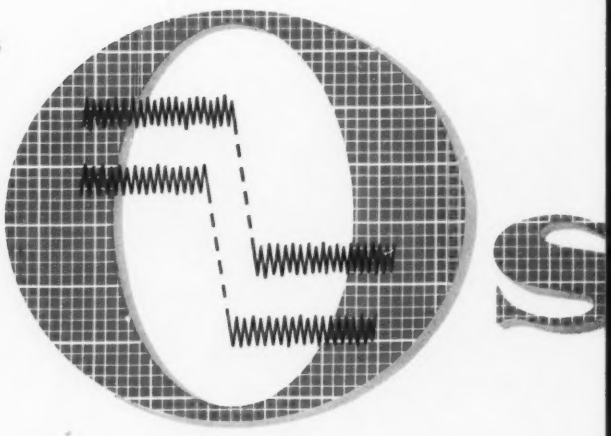

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BY-EFFECTS OF THREE OTHER GANGLIONIC-BLOCKING AGENTS[6,7,8] COMPARED WITH THOSE OF OSTENSIN[1,9]

	Other Agents	OSTENSIN
Constipation	59-69% of patients	5% of patients
Postural hypotension	33-59% of patients	37% of patients
Visual disturbances	42-50% of patients	34% of patients
Dry mouth	38-41% of patients	15% of patients

"Of particular interest has been the virtual absence of constipation despite adequate blood pressure control. This finding suggests a lower risk of paralytic ileus. . . ."[1]

Supplied: Tablets, scored, 20 and 40 mg., vials of 100.

1. Dunsmore, R.A., et al.: Am. J. M. Sc. *236*:483 (Oct.) 1958. 2. Blaquier, P., et al.: Univ. Michigan M. Bull. *24*:409 (Oct.) 1958. 3. Smirk, F.H.: Submitted for publication. 4. Janney, J.F.: Submitted for publication. 5. Council on Drugs, A.M.A.: J.A.M.A. *166*:640 (Feb. 8) 1958. 6. Freis, E.D., and Wilson, I.M.: Circulation *13*:856 (June) 1956. 7. Moyer, J.H., et al.: A.M.A. Arch. Int. Med. *98*:187 (Aug.) 1956. 8. Moyer, J.H., et al.: Am. Pract. & Dig. Treat. *7*:1765 (Nov.) 1956. 9. Dunsmore, R.A. In Tislow, R.F., et al.: Scientific Exhibit. Presented at Annual Convention of A.M.A., San Francisco, June 23-27, 1958.

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Ganglionic blockade with fewer and milder by-effects

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H. K., 44 years old, with history of heavy drinking. Previously hospitalized in 1954, with diagnosis of Laennec's cirrhosis. Admitted on 3/3/59, patient complained of swollen abdomen, swelling in both legs and exertional dyspnea.

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Treatment: Mercurial diuretic on 3/3 and 3/4, followed by Esidrix, 50 mg. b.i.d., from 3/5 to 3/23 when patient signed out of hospital. Esidrix induced copious diuresis resulting in almost complete disappearance of edema.

Supplied: Esidrix *Tablets,* 25 mg. (pink, scored) and 50 mg. (yellow, scored); bottles of 100 and 1000.

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KEEPS THE MIND OFF THE STOMACH

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES:

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greater specificity
of tranquilizing action
—divorced from such
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anti-emetic action
—explains why

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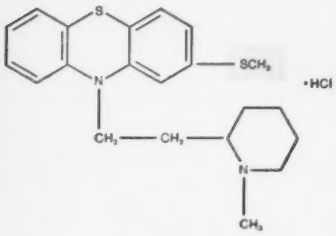
is virtually free of such toxic effects as • jaundice • Parkinsonism • blood dyscra

"Thioridazine [MELLARIL] is as effective as the best available phenothiazine, but w appreciably less toxic effects than those demonstrated with other phenothiazines. . . . Th drug appears to represent a major addition to the safe and effective treatment of a wi range of psychological disturbances seen daily in the clinics or by the general practitioner

a new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical ($S\text{-}CH_3$) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:

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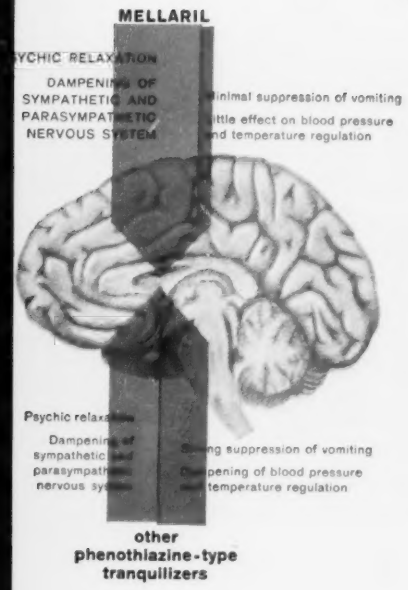
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PSYCHIC RELAXATION
DAMPENING OF SYMPATHETIC AND PARASYMPATHETIC NERVOUS SYSTEM
Minimal suppression of vomiting
Little effect on blood pressure and temperature regulation
Psychic relaxation
Dampening of sympathetic and parasympathetic nervous system
Suppression of vomiting
Dampening of blood pressure and temperature regulation
other phenothiazine-type tranquilizers

2 Less "spill-over" action to other brain areas – hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.

3 A notable absence of extrapyramidal stimulation.

4 Lack of impairment of patient's normal drive and energy.

5 Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.

Indication	Usual Starting Dose	Total Daily Dosage Range
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MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
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CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

llaril Tablets, 10 mg., 25 mg., 100 mg.

eld, A. M.: Scientific Exhibit, American Academy General Practice, San Francisco, April 6-9, 1959

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Why is the three-day biliary flush recommended after cholecystectomy?

To remove stones and debris frequently present in the common duct when choledochostomy has not been done.

Source: Best, R. R.; Rasmussen, J. A., and Wilson, C. E.: A.M.A. Arch. Surg. *67*:839, 1953.

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*Adapted from Best, R. R., and others: **ibid.**

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in medical management—"... also recommended for patients with a clinical history of biliary tract disease when gallbladder disease has not been confirmed."[2]

1. Refresher Article: M. Times *85*:1081 (Oct.) 1957.
2. Best, R. R.: Mod. Med. *25*:264 (March 15) 1957.

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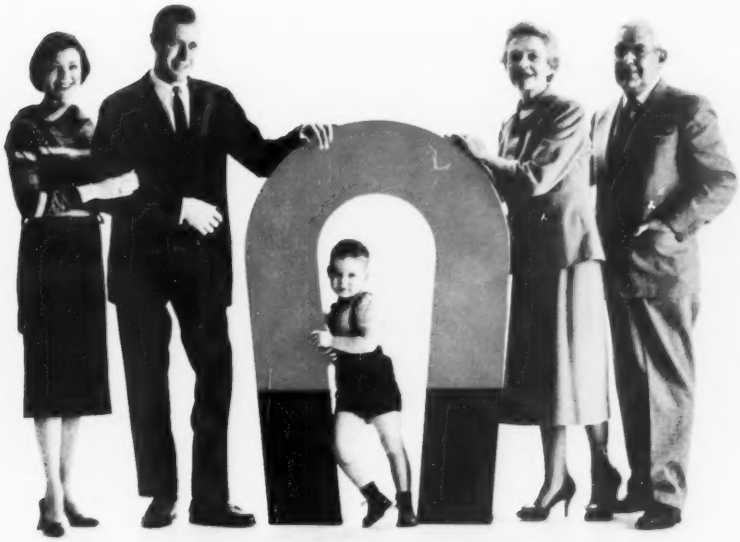

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Keyes, J.W. and Berlacher, F.J.: J.A.M.A. 169:109, (Jan. 10) 1959.

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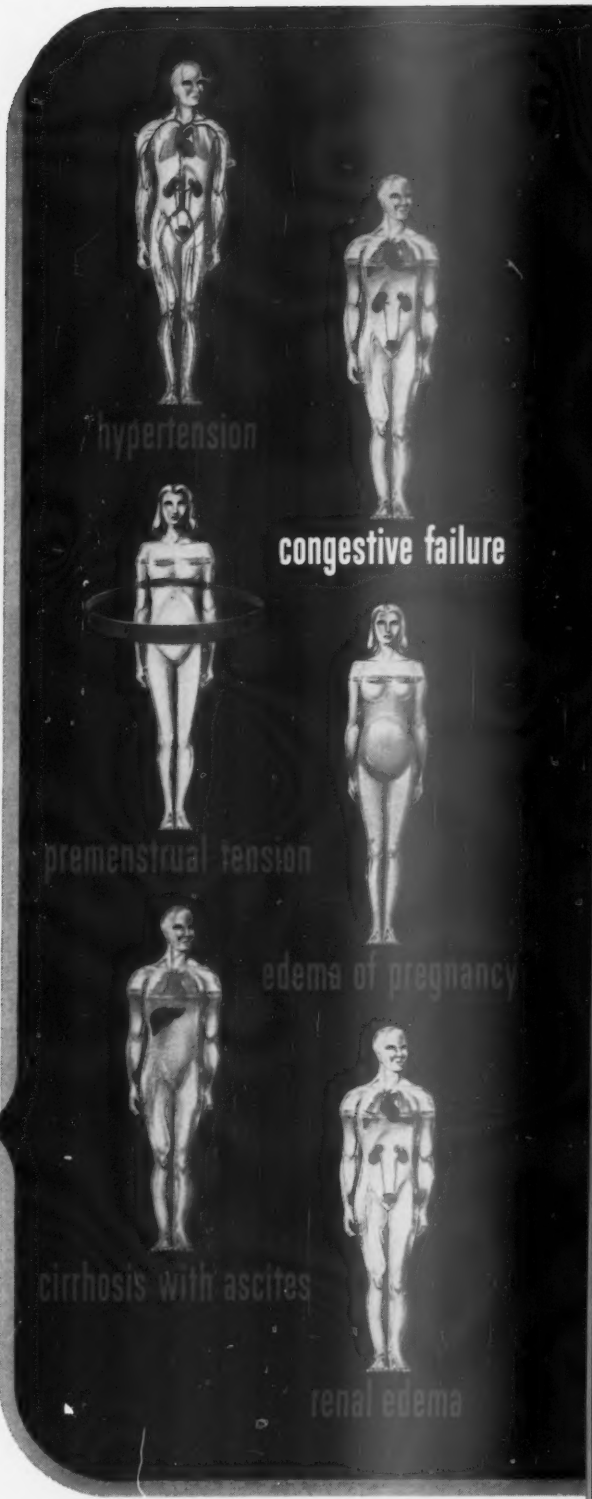
a continuing and consistently outstanding record of safety and efficacy in:



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safely controls the "target symptoms" of emotional stress with the smallest effective dosage of any neuroleptic* agent (0.25 mg. b. i. d.)

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virtually free from side effects at the recommended dosage level

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"Fluphenazine (PERMITIL) the latest and most potent phenothiazine tranquilizer was administered from 3 to 20 months to 200 ambulatory and hospitalized patients representing a full spectrum of diagnostic classifications including psychosomatic disorders. Fractional doses of this drug rapidly produced improvement in 74% of these patients while causing a minimum of sedative, autonomic and endocrine effects which disappeared as treatment continued. . . . Patient acceptance of this compound was excellent because its prescription facilitated rather than interfered with the efficient performance of daily tasks. The physician who masters the art of fluphenazine use can treat a widened spectrum of target symptoms, safely and effectively."[2]

Now,
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a phenothiazine
anti-anxiety agent

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designed specifically for
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A Factor to Consider in Phenothiazine Therapy

"The more potent the phenothiazine derivative the fewer the side effects it produces, because less of the chemical is needed to effect behavioral and therapeutic changes."[2]

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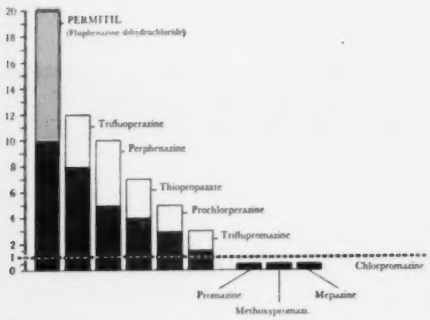

Adapted from Ayd, F. J., Jr.[3]

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Available as Tablets, 0.25 mg., bottles of 50 and 500.

References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J., Jr.: Fluphenazine: its spectrum of therapeutic application and clinical results in psychiatric patients, Current Therapeutic Research, 1:41 (Oct. 15) 1959. 3. Ayd, F. J., Jr.: The current status of major tranquilizers, in press.

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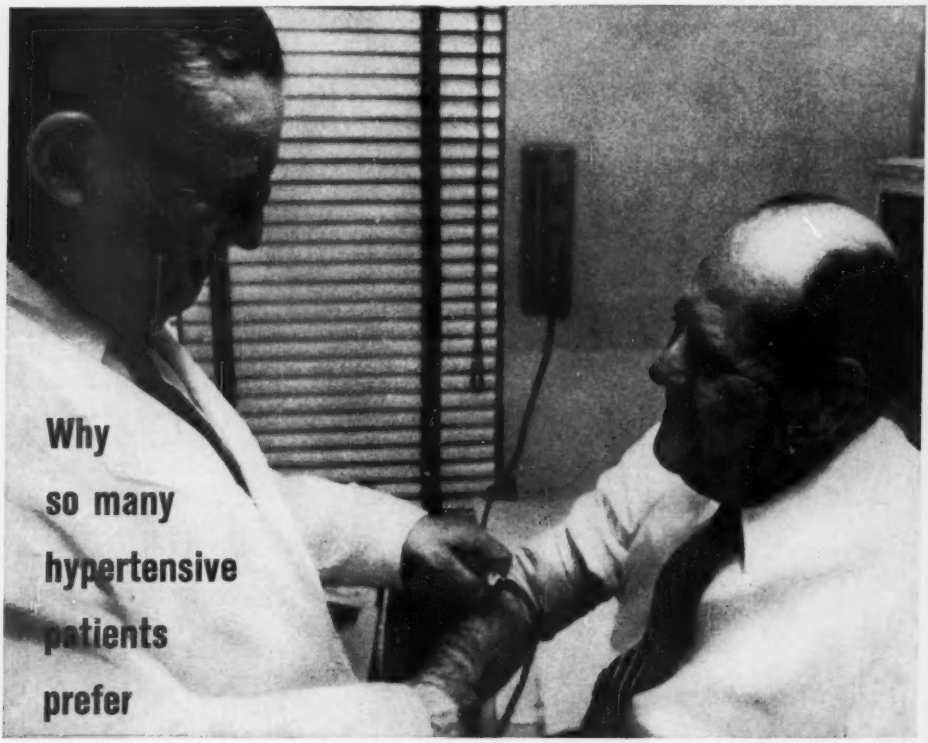

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. **169**:1609 (April 4) 1959.

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Composition: Each 15A Supprette contains ½ gr. Powdered Opium, U.S.P.—¼ gr. Extract Belladonna—Each 16A Supprette contains 1 gr. Powdered Opium, U.S.P.—¼ gr. Extract Belladonna

Packaged 12 Suppettes to the jar. •Narcotic Order Required.

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Mathematically, of course, 1 plus 1 does not equal three, but the Cambridge Audio-Visual Heart Sound Recorder makes a seeming paradox—true! The simultaneous, instantaneous viewing and hearing of the heart sounds give more than the simple sum of the two . . . they provide the plus factor!

With this most versatile instrument, the Doctor hears the heart sounds faithfully reproduced through binaural ear phones while viewing the pattern on the long persistence screen of a cathode ray tube.

Any portion of the heart sounds may be permanently recorded upon thin magnetic discs. These paper-thin but durable records may be filed as part of a patient's history or mailed for consultation. They may be "played back" (both heard and viewed) for study or for consultation.

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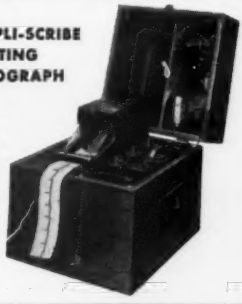
Provides the Cardiologist, Clinic or Hospital with a portable direct writing Electrocardiograph of utmost usefulness and accuracy. Size 10¾" x 10⅜" x 11". Weighs 28 pounds with all accessories.



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CARDIAC DIAGNOSTIC INSTRUMENTS

Lifts depression...

An emotionally balanced patient
Thanks to your treatment and the help of Deprol, her depression is relieved and her anxiety and tension calmed. She eats well, sleeps well, and can return to her normal activities.

as it calms anxiety!

Deprol helps balance the mood by lifting depression as it calms related anxiety

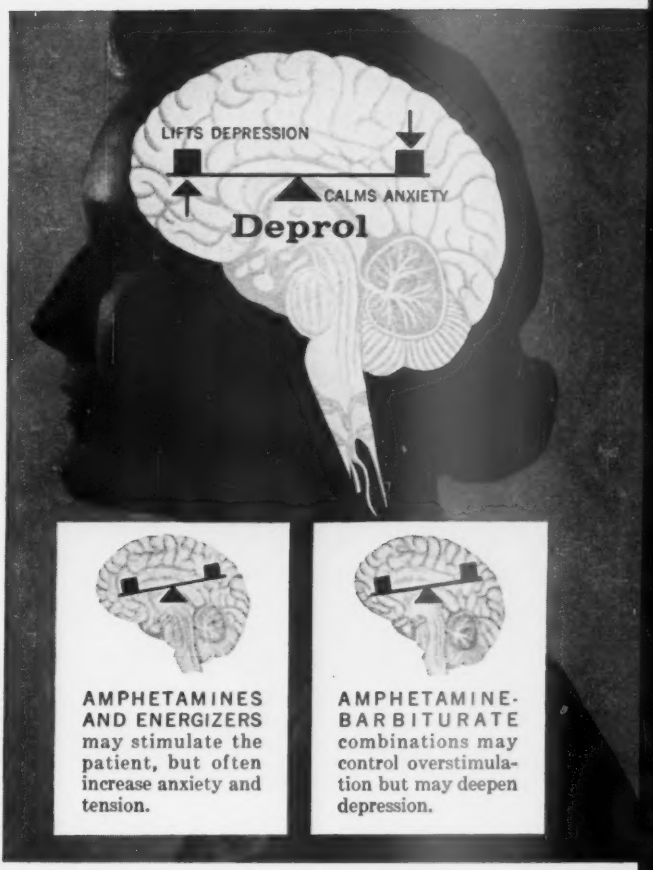
No "seesaw" effect of amphetamine-barbiturates and energizers

While amphetamines and energizers may stimulate the patient—*they often aggravate anxiety and tension.* And although amphetamine-barbiturate combinations may counteract excessive stimulation—*they often deepen depression.*

In contrast to such "seesaw" effects, Deprol lifts depression as it calms anxiety—both at the same time.

Safer choice of medication than untested drugs

Deprol does not produce hypotension, liver damage, psychotic reactions or changes in sexual f[illegible]nction.


LIFTS DEPRESSION
CALMS ANXIETY
Deprol
AMPHETAMINES AND ENERGIZERS may stimulate the patient, but often increase anxiety and tension.
AMPHETAMINE-BARBITURATE combinations may control overstimulation but may deepen depression.

BIBLIOGRAPHY: 1. Alexander, L.: Chemotherapy of depression—Use of meprobamate combined with benactyzine (2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A. 166:1019, March 1, 1958. 2. Bateman, J. C. and Carlton, H. N.: Deprol as adjunctive therapy for patients with advanced cancer. Antibiotic Med. & Clin. Therapy. In press, 1959. 3. Bell, J. L., Tauber, H., Santy, A. and Pulito, F.: Treatment of depressive states in office practice. Dis. Nerv. System 20:263, June 1959. 4. McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B.: Treatment of depression—New technics and therapy. Am. Pract. & Digest Treat. In press, 1959. 5. Pennington, V. M.: Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. 7:656, Aug. 1959. 6. Rickels, K. and Ewing, J. H.: Deprol in depressive conditions. Dis. Nerv. System 20:364, (Section One), Aug. 1959. 7. Ruchwarger, A.: Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia 28:438, Aug. 1959. 8. Settel, E.: Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959.

Deprol®

DOSAGE: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.

COMPOSITION: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

SUPPLIED: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

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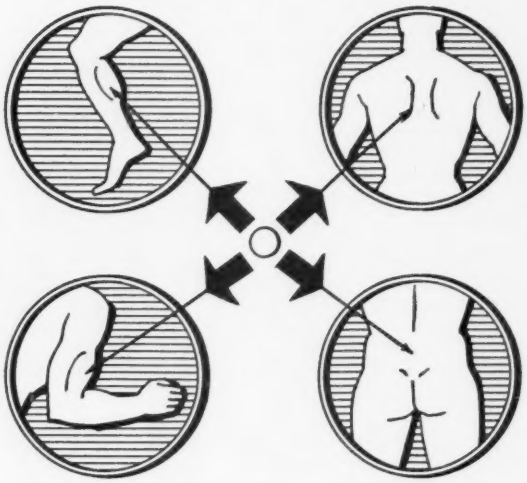
CD-559

In Skeletal Muscle Spasm

Norflex™*

orphenadrine citrate

acts quickly to restore mobility and afford relief of associated pain



Spasmolytic action is prompt, and only the muscle in spasm is relaxed...the patient is spared impairment of general muscle tonus.

Patients can cooperate readily...the dosage is easily remembered: just one tablet b.i.d.

Compare this with other spasmolytics requiring from 4 to 30 tablets per day.

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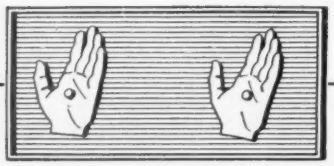

Only one tablet b.i.d. for all adults, regardless of age, weight, sex, or spasm severity.

Riker Northridge, California

*Trademark U. S. Patent No. 2,567,351
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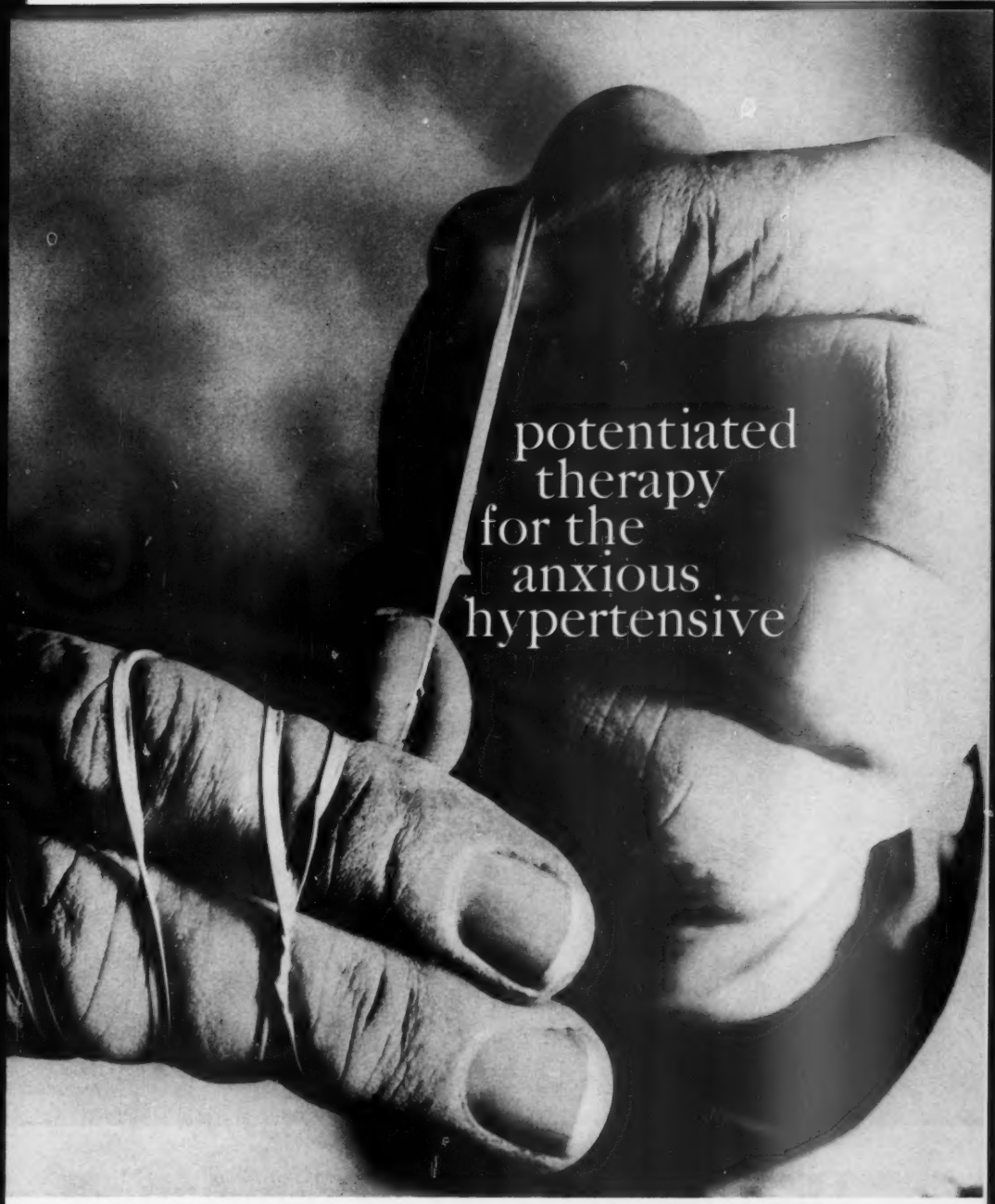

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THE doctor's room in the hospital is used for a variety of reasons. Most any morning, you will find the internist talking with the surgeon, the resident discussing a case with the gynecologist, or the pediatrician in for a cigarette. It's sort of a club, this room, and it's a good place to get the low-down on "Premarin" therapy.

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Beaser, S. B.: Ann. New York Acad. Sc. 74:701, 1959.

also successful when dietary control proves impractical...and when other oral therapy has failed

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BUTISOL® effectively reduces nervous irritability and tension—without causing apathy and irresponsibility. In a recent study of six widely used sedatives and tranquilizers, Butisol showed "The highest therapeutic index of any drug studied for control of daytime anxiety and insomnia. The lowest incidence of side effects, and least likelihood of cumulative toxicity."[1]

TABLETS · REPEAT-ACTION TABLETS · ELIXIR · CAPSULES

1. Batterman, R. C.; Grossman, A. J.; Mouratoff, G. J., and Leiter, P.: A Clinical Re-evaluation of Daytime Sedatives, Scientific Exhibit, Annual Meeting of AMA, San Francisco, Cal.; June 23-27, 1958.

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in acute superficial thrombophlebitis

"A one-week course of therapy is generally sufficient to produce satisfactory resolution of the inflammatory process without recurrence."

Orbach, E. J.: J. Internat. Coll. Surgeons 31:165, 1959.

in arthritis and allied disorders

"Patients who experienced major improvement had prompt and almost complete relief of pain and stiffness, which could be maintained on a small maintenance dose."

Graham, W.: Canad. M.A.J. 79:634, (Oct. 15) 1958.

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BUTAZOLIDIN® (brand of phenylbutazone): Red-coated tablets of 100 mg.

BUTAZOLIDIN® Alka: Orange and white capsules containing BUTAZOLIDIN 100 mg.; dried aluminum hydroxide gel 100 mg.; magnesium trisilicate 150 mg.; homatropine methylbromide 1.25 mg.

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In prophylaxis of angina pectoris

"The best results..."

"The best results... in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE]...." Russek[1] so reported using double-blind methods in an important new study of pentaerythritol tetranitrate, a placebo, meprobamate, and EQUANITRATE.

EQUANITRATE reduces the frequency and severity of attacks and controls angina-triggering emotions.

Supplied: EQUANITRATE **10** (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE **20** (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

1. Russek, H.I.: Am. J. Cardiol. *3*:547 (April) 1959.

Equanitrate*

Meprobamate and Pentaerythritol Tetranitrate, Wyeth

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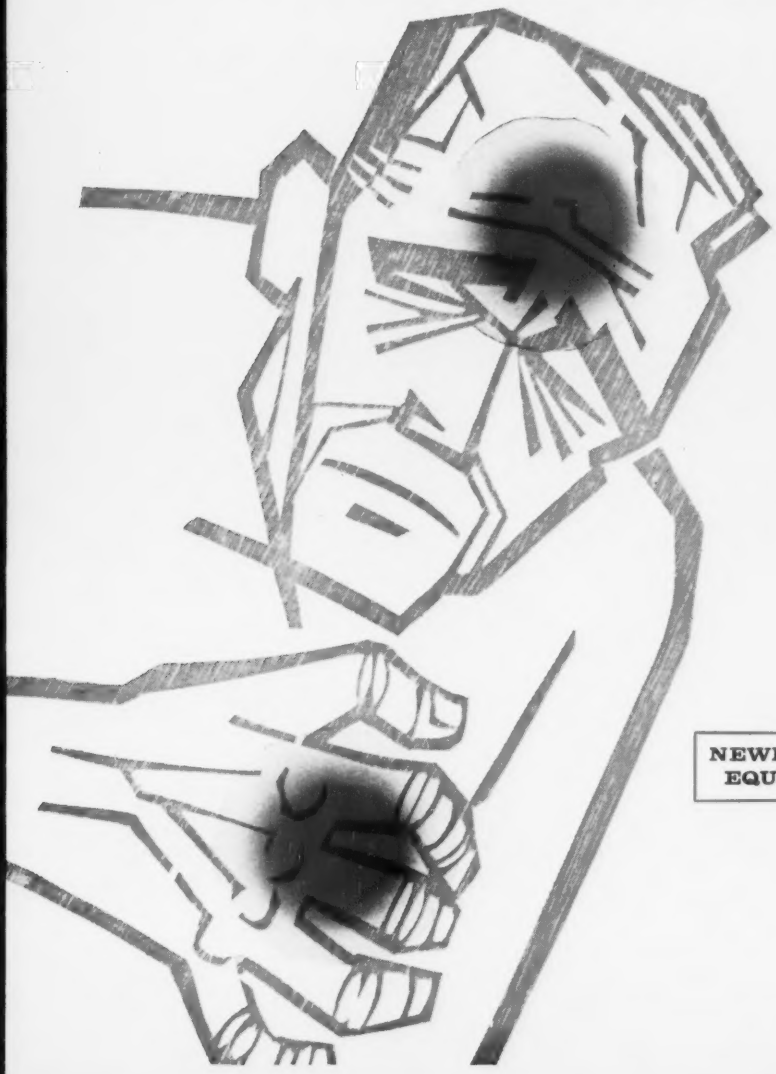

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EQUANITRATE 20

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confirmed in clinical study:

maximum saluretic effect with minimum potassium loss

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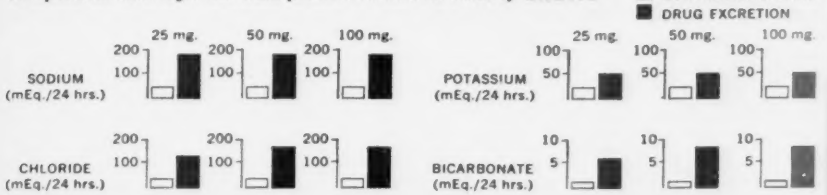
(HYDROCHLOROTHIAZIDE, ABBOTT)

your most potent means when the end is saluresis

Studying **ORETIC** which they describe as "*. . . a significant advance in development of diuretic agents of greater potency without increasing toxicity. . .*" the investigators tested, among other properties of the compound, its effect on urinary electrolyte excretion.

Drug was given at 25-, 50- and 100-mg. doses to five patients, all previously having congestive heart failure but currently free of signs of edema. Urine was analyzed six times during a 24-hour study period, with attention given to the major electrolytes—sodium, potassium, bicarbonate and chloride:

Comparative electrolyte excretion patterns at various doses of **ORETIC**



The investigators said:

"Comparative electrolyte excretion effects at various doses of **ORETIC** show a proportional increase in sodium and chloride within the significant dose range and demonstrate that additional drug has no significant action. The continued relatively small potassium and bicarbonate excretion, even with maximum saluretic effects, is clearly demonstrated."

ORETIC, indicated for edema and hypertension, is supplied in 25- and 50-mg. tablets, bottles of 100 and 1000.

and remember—in many cases Oretic permits relaxation of the low-salt patient's rigid diet

Bibliographical Note: The investigators quoted have published their findings in the September, 1959 issue of *Current Therapeutic Research*. The study, entitled CLINICAL PHARMACOLOGIC OBSERVATIONS ON ORETIC, A NEW ORALLY ACTIVE DIURETIC AGENT, can be found in that publication on pages 26 through 33.

ABBOTT

Oretic—Trademark for Hydrochlorothiazide, Abbott

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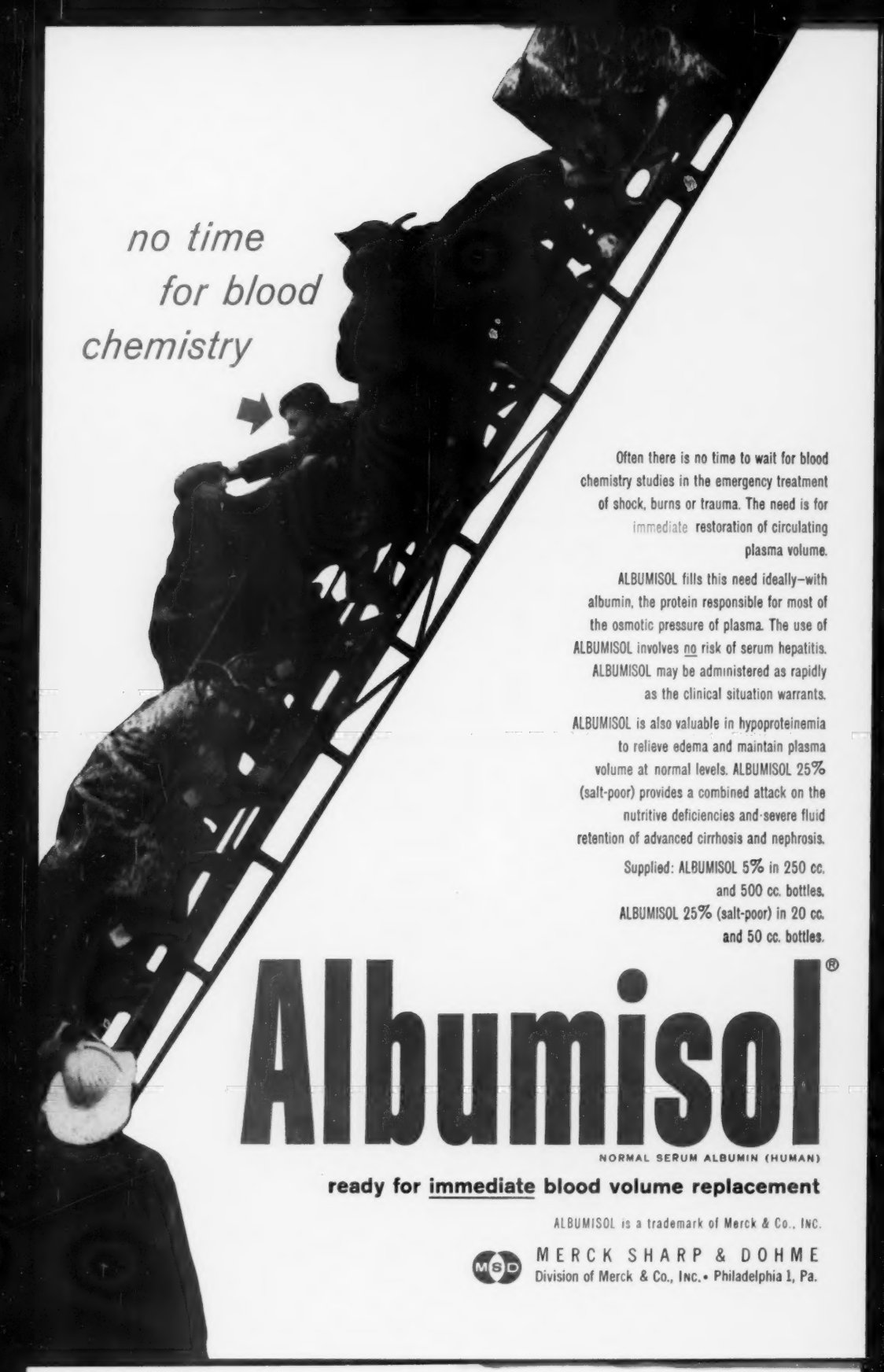

Often there is no time to wait for blood chemistry studies in the emergency treatment of shock, burns or trauma. The need is for immediate restoration of circulating plasma volume.

ALBUMISOL fills this need ideally—with albumin, the protein responsible for most of the osmotic pressure of plasma. The use of ALBUMISOL involves no risk of serum hepatitis. ALBUMISOL may be administered as rapidly as the clinical situation warrants.

ALBUMISOL is also valuable in hypoproteinemia to relieve edema and maintain plasma volume at normal levels. ALBUMISOL 25% (salt-poor) provides a combined attack on the nutritive deficiencies and severe fluid retention of advanced cirrhosis and nephrosis.

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ready for immediate blood volume replacement

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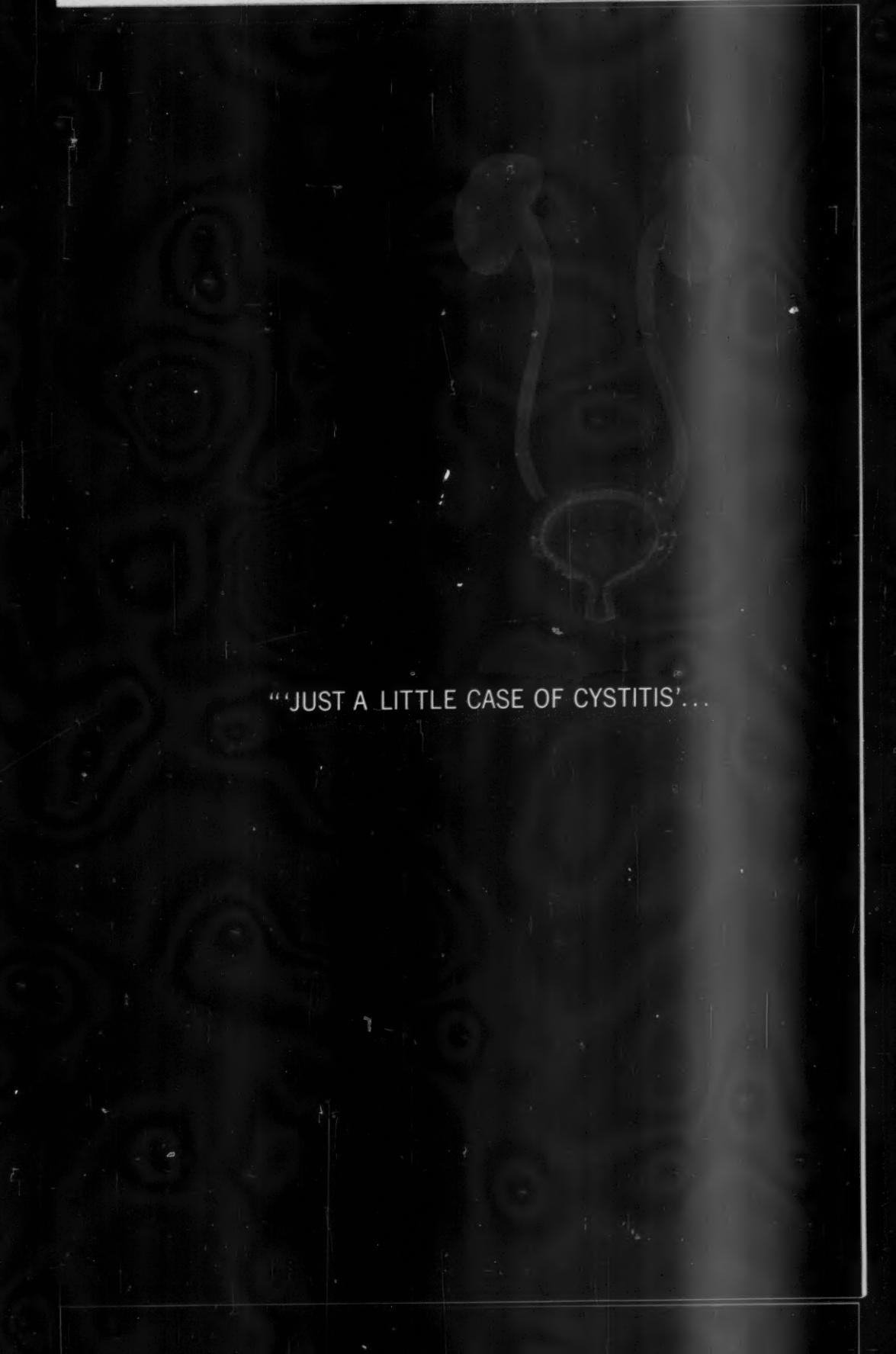
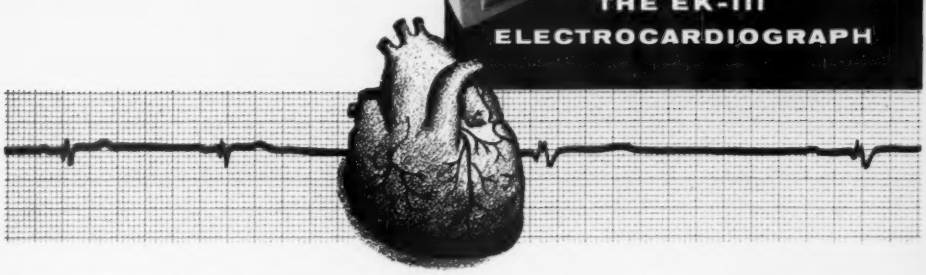

"'JUST A LITTLE CASE OF CYSTITIS'...

Burdick

DUAL-SPEED CARDIOGRAPHY

for more accurate diagnosis

THE EK-III ELECTROCARDIOGRAPH



The importance of dual-speed cardiography is emphasized in this statement from a report* of the Committee on Electrocardiography of the American Heart Association: "It has become increasingly clear that the more or less standard speed of 25 mm. per second incorporated in most instruments makes it difficult on occasion to resolve certain diagnostic details of rapid electrocardiographic deflections." It points out that "a speed of 50 mm. per second appears to be particularly useful."

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Circulation, Vol. X, No. 4

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"'Just a little case of cystitis' may actually have already involved the kidney parenchyma before the bladder became infected."[1]

"The first evidence of inflammatory disease of kidney or prostate often is vesical irritability."[2]

WHEN THE SYMPTOM IS CYSTITIS

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for rapid control of infection throughout the G. U. system

Rapid bactericidal action against a wide range of gram-positive and gram-negative bacteria including organisms such as staphylococci, Proteus and certain strains of Pseudomonas, resistant to other agents ■ actively excreted by the tubule cells in addition to glomerular filtration ■ negligible development of bacterial resistance after 7 years of extensive clinical use ■ excellent tolerance—nontoxic to kidneys, liver and blood-forming organs ■ safe for long-term administration

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REFERENCES: 1. Editorial: J.M.A. Georgia 46:433, 1957. 2. Colby, F. H.: Essential Urology, Baltimore, The Williams & Wilkins Co., 1953, p. 330.

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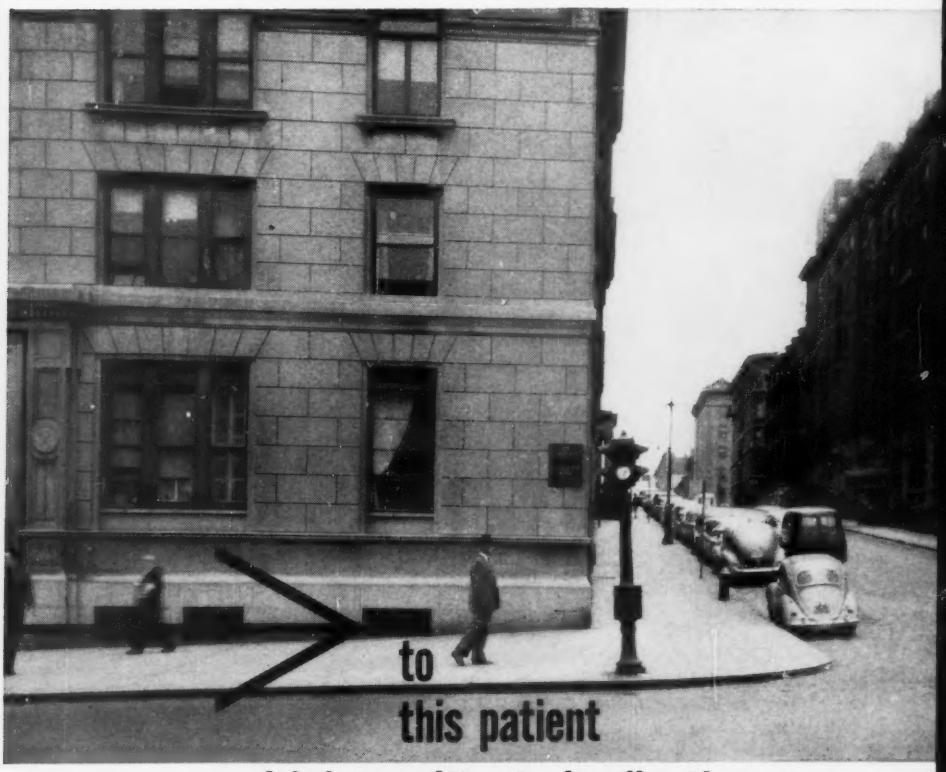

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now...**arlidin**

makes the blocks so much shorter...
he can walk many more of them in comfort

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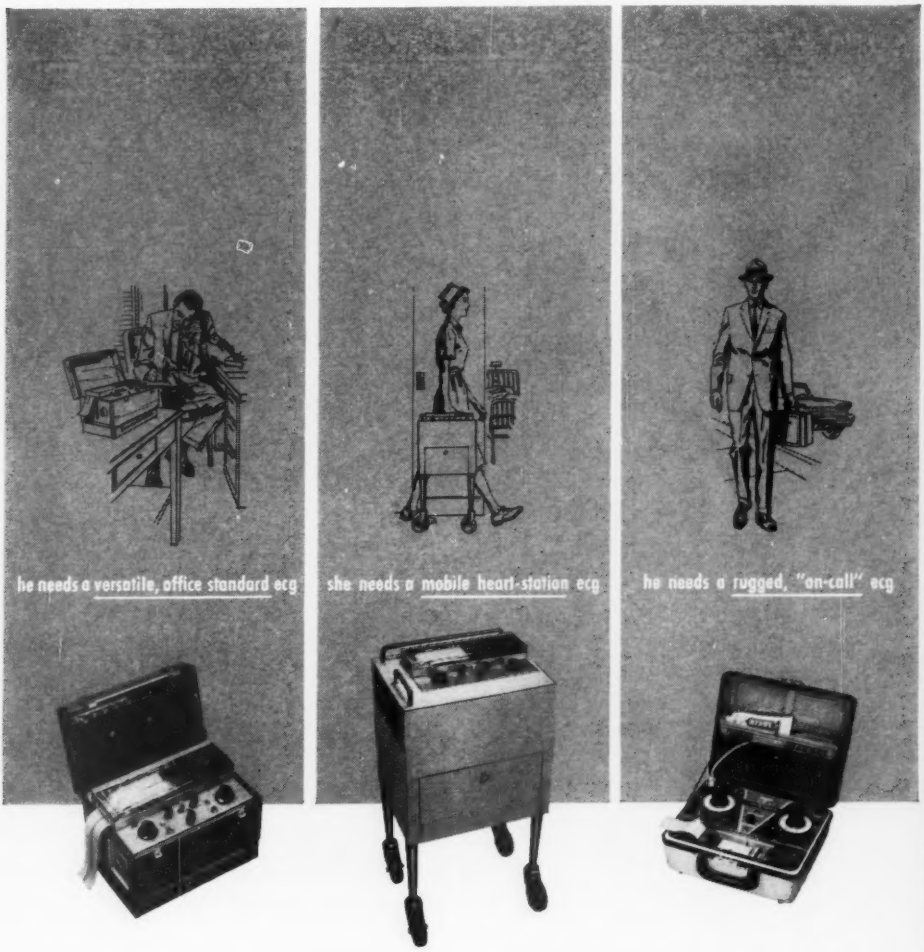

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parkinsonism — dyskinesia — akathisia

MUSCULAR SPASTICITY NOT RELATED TO PARKINSONISM

ACTION	Frequently diminshes akinesia, rigidity, and tremor with subsequent improvement in coordinated movement, gait, and posture. Masklike face disappears. Salivation and oily skin are decreased. Oculogyric crises are often lessened in intensity and frequency.
SIDE EFFECTS	Minimum (mainly dry mouth or blurred vision).
DOSAGE	**Individual adjustment of dosage is necessary in all instances.** Dose range extends from 2 mg. to 24 mg. daily, in divided doses.
AVAILABLE	Supplied as the hydrochloride salt, 2 mg. bisected tablets, bottles of 100 and 1000.

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Dust is a principal offender in allergies of the respiratory tract. It cannot be avoided — and the dust-allergic patient requires medical attention. POLARAMINE — the closest to a perfect antihistamine — is the closest to a perfect solution for the problem of the patient suffering from irritating nonseasonal allergens. POLARAMINE offers swift, sure, safe action with these outstanding advantages —

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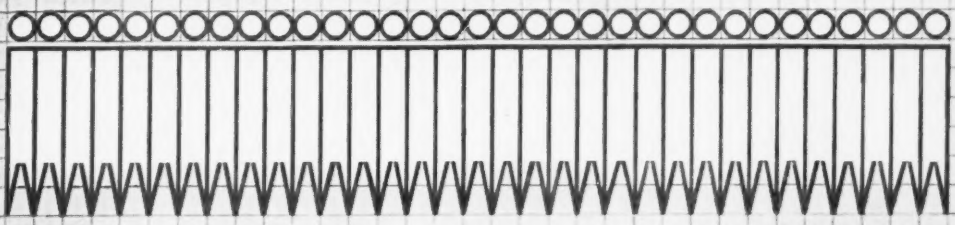
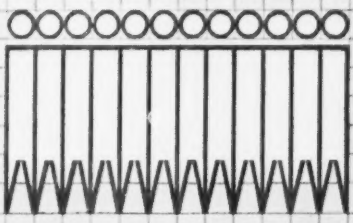
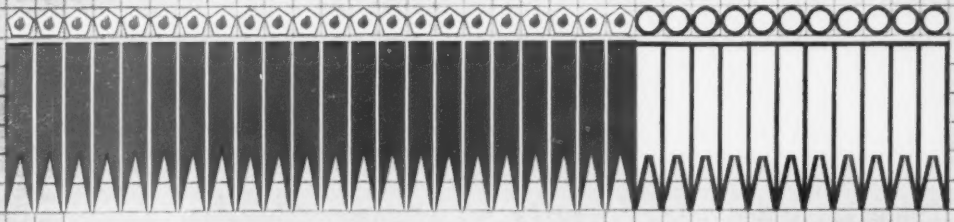
DEXAMETHASONE

treats more patients more effectively...

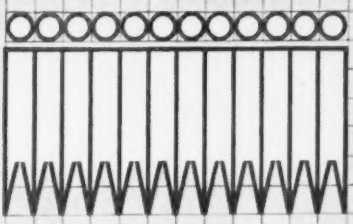


Of 45 arthritic patients
who were refractory
to other corticosteroids*





22 were successfully
treated with **Decadron**[1,2]



1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

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SYSTEMIC LUPUS ERYTHEMATOSUS AFTER "IDIOPATHIC" THROMBOCYTOPENIC PURPURA: A REVIEW.

A study of systemic lupus erythematosus occurring after 78 splenectomies for "idiopathic" thrombocytopenic purpura, with a review of the pertinent literature * †

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WE have previously emphasized the close relationship between idiopathic thrombocytopenic purpura (I.T.P.) and systemic lupus erythematosus (S.L.E.), and have suggested that I.T.P. is often a prodrome of the larger syndrome. Actually, purpura has been known in systemic lupus erythematosus (hereafter designated S.L.E.) since early descriptions of the disease.[28, 39, 40, 41] Kaposi [28] was perhaps the first to remark on the association of lupus and purpura. Tumulty [51] and Harvey,[23] in their reviews of the history of S.L.E., have stressed Osler's understanding of the systemic nature of the disease, which he called "erythema exudativum multiforme," and his awareness of the occurrence of purpura both with and without skin eruption.

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Keil [29] noted that purpura in lupus was the result of different mechanisms, including vascular factors, azotemia and thrombocytopenia. The hematologic aspects of S.L.E. have been increasingly stressed in recent years.[6]

Although thrombocytopenia is frequent in S.L.E., overt thrombocytopenic purpura is comparatively rare. In table 1A are compiled 274 cases of S.L.E. where sufficient data relating to platelet counts were given by the authors; of these, 82 (30%) had thrombocytopenia. The incidence of overt purpura with thrombocytopenia was much less. Thus, in 380 cases of S.L.E. reported in seven series (table 1B), 29 cases of thrombocytopenic

TABLE 1

A. Incidence of Thrombocytopenia in S.L.E.

	No. with Thrombocytopenia	No. with S.L.E.	% of S.L.E. with Thrombocytopenia
Marten[23]	7 (66 chronic discoid)	77	9
Johnson[26]	4	12	33
Michael[34]	43	83	52
Harvey[23]	23	86	27
Shearn[46]	5	16	31
Combined Series	82	274	30%

B. Incidence of Thrombocytopenic Purpura in S.L.E.

	No. with Thrombocytopenic Purpura	No. with S.L.E.	% of S.L.E. with Thrombocytopenic Purpura
Marten[23]	1 (66 chronic discoid)	77	1.3
Johnson[26]	2	12	17
Michael[34]	2	83	2.4
Shearn[46]	4	34	12
Dubois[12]	6	62	10
Harvey[23]	12	86	14
Gold[20]	2	26	8
Combined Series	29	380	7.6%

purpura (7.6%) were recorded. It should be realized that these are very rough figures, derived from several series of cases collected with different approaches. Thus, most of Marten's cases had discoid lupus, and Michael's series showed a very high percentage of thrombocytopenia probably because an effort was made to include all cases that had thrombocytopenia at some time in the course of the systemic disease.

Occasionally S.L.E. presents itself with thrombocytopenic purpura as the initial and predominant manifestation of the disease, with other features either not present or minor in character. These cases are often indistinguishable from "idiopathic thrombocytopenic purpura." Harvey et al.[23] collected 13 cases of this type from the literature and added nine from their own series. In six of these 22 cases there was no other manifestation in any

way suggestive of S.L.E. Nine others had skin lupus. Other manifestations (in some instances more than one in the same patient) suggestive of S.L.E. occurring in these cases were: nephritis, one; arthritis or arthralgia, seven; urticaria, three; unexplained fever, two; pleurisy, one. All 22 cases were considered to be examples of I.T.P. when first seen. With the increasing awareness of I.T.P. as a major manifestation of S.L.E.,[9, 45] it is likely that some of these cases might now be at least suspected of having S.L.E.

The study of any one of the many abnormalities found in systemic lupus, certainly a protean disease, can be approached from several different directions. Thus, Eversole[17] and Rich[44] studied spleens from cases of I.T.P. as a source of material (see further below under discussion of periarterial fibrosis in the spleen), and Moore[36] analyzed a series of cases showing chronic false-positive serologic tests for syphilis. In the present study we have reviewed our splenectomized cases of I.T.P. as a source of case material. Although previous studies have been made of the incidence of thrombocytopenia in S.L.E., we have found no report of an attempt to determine the incidence of S.L.E. in a series of cases of idiopathic thrombocytopenic purpura.

Method and Materials

Our approach to this problem was through reëvaluation of our splenectomized cases of I.T.P. This approach tended to eliminate the cases of "acute" I.T.P., which as a rule are self-limited. More often than not, such cases are associated with some acute infectious disease, as chickenpox, the use of a viral prophylactic agent (poliomyelitis vaccine, Asiatic "flu" vaccine, etc.), or some drug such as quinidine. It was standard practice on this service until 1955[45] to perform splenectomies on all cases of I.T.P. that had exhibited thrombocytopenia for four months or more; these cases were considered to be chronic.[24] Splenectomy was done in the acute cases only if temporizing measures seemed to be endangering life due to persistent, severe bleeding. In recent years, all of our cases have been treated with prednisone, prednisolone or triamcinolone,[45] splenectomy being reserved as a measure of last resort. The present study is limited to splenectomized cases. Sufficient time has not yet elapsed to evaluate the incidence of S.L.E. in corticosteroid-treated cases (see further discussion below). The splenectomized series included practically all of our "chronic" cases of I.T.P. up to late 1955, although a few "acute" cases were included. These cases were consecutive and unselected, and of a number sufficient to afford at least suggestive incidence figures.

Letters of recall were sent to all patients whose spleens had been removed for I.T.P. Those who responded were reëxamined, their records reviewed and various hematologic studies done. These included a "complete" blood count including the platelet count, Coombs' test, Hinton test and L.E. test.

The patients fell into two groups. The first consisted of those cases splenectomized prior to July, 1949. This group of 27 cases is the one reported in our earlier paper.[24] The second group of 51 cases was splenectomized after July 1, 1949. The response to letters in the first group was very poor, and a representative sample was therefore not obtained. Since an adequate follow-up was obtained in only 12 of the 27 cases, they will therefore not be included in the incidence studies, although several cases of S.L.E. from this group will be reported for their interest. In the second group, an adequate follow-up was obtained in 44 of the 51 cases. Four of the 44 had "acute" I.T.P. and the rest were "chronic" cases. None of the acute cases, however, showed any evidence of S.L.E. They have not, however, been excluded from the study, because splenectomy was performed before sufficient time had elapsed to demonstrate that they would not have become chronic. Furthermore, we have no evidence that S.L.E. may not follow "acute" I.T.P., at least in the type which is not associated with a definite etiologic factor such as a drug or an infection.

Because of their unusual interest, we are presenting two additional cases of "definite" S.L.E. (cases 9 and 10) who were diagnosed as I.T.P. but in whom splenectomy had been performed at other hospitals before they were seen by us (and were thus not included in the series). In neither case were there antecedent manifestations of S.L.E. before splenectomy, but definite evidence of S.L.E. developed later.

Diagnostic Criteria for S.L.E.

The cases of S.L.E. have been divided into three diagnostic categories: (1) "definite" S.L.E., (2) "probable" S.L.E., and (3) "possible" S.L.E. In brief, a "definite" case was one that had, in addition to thrombocytopenic purpura, at least one of the "diagnostic" manifestations of lupus erythematosus: discoid lupus, well marked onion-skin lesions in the spleen, positive L.E. cell test, or such a conglomeration of lesser manifestations as to make the diagnosis inescapable. A "probable" case was one that did not exhibit one of these diagnostic criteria, but yet had several "major" or "minor" evidences of S.L.E., or presented "diagnostic" manifestations in lesser degree. A "possible" case was one that showed at least one of the commonly associated minor manifestations of S.L.E., in addition to I.T.P. Actually, we feel that the occurrence of I.T.P. alone is almost sufficient in and of itself for the diagnosis of "possible" S.L.E. Table 2 gives a list of the manifestations of S.L.E. as we have divided them into (1) diagnostic, (2) major, and (3) minor groups.

There is, of course, no substitute for clinical judgment in the diagnosis of S.L.E. We have offered these criteria to show the basis for our diagnosis of S.L.E. The validity of discoid lupus, positive L.E. tests and onion-skin lesions in the spleen as diagnostic criteria will be discussed in detail below.

TABLE 2

Diagnostic Manifestations of S.L.E. (which many authorities consider to be diagnostic of S.L.E. occurring alone, and doubly so when combined with I.T.P.):

(1) Discoid lupus
(2) Positive L.E. cell test
(3) Well marked splenic perivascular fibrosis
(4) "Wire-loop" lesions in the kidneys

Major Manifestations of S.L.E. (not diagnostic in themselves, but occurring singly are sufficient to raise a strong suspicion of S.L.E.):

(1) "Idiopathic" thrombocytopenic purpura (I.T.P.)
(2) Coombs' positive hemolytic anemia
(3) Arthritis
(4) Nephritis

Minor Manifestations of S.L.E. (not diagnostic, but so frequently associated with S.L.E. that they serve to enhance the diagnosis if a diagnostic or a major manifestation is present; arouses suspicion of S.L.E. when several occur together):

(1) Hyperglobulinemia
(2) Urticaria
(3) Rapid blood sedimentation rate
(4) Splenomegaly
(5) False-positive serologic test for syphilis
(6) Pleuritis and/or pericarditis
(7) Unexplained fever
(8) Raynaud's phenomenon
(9) Leukopenia
(10) Arthralgias

RESULTS

Incidence of S.L.E. in 51 Consecutive Splenectomized Cases of I.T.P.: The group of 51 consecutive splenectomized cases of I.T.P. (post-July, 1949, series) included four "acute" cases. None of the latter developed S.L.E. Seven cases with an inadequate follow-up were lost to follow-up within one month after splenectomy. Since their spleens were, however, available for examination, we have not felt free to eliminate them from consideration. The fact that all 51 cases are included generally lowered the percentage of positive results, thereby increasing their significance.

"Definite" S.L.E. was diagnosed in eight (cases 1–8) of the 51 cases of splenectomized I.T.P.; "probable" S.L.E. in two (cases 15 and 16), and "possible" S.L.E. in six (cases 17–22). Thus 15.7% were examples of "definite" S.L.E., 19.6% were "definite" or "probable" S.L.E., and 31.4% were "definite," "probable" or "possible" S.L.E. In other words, of 51 splenectomized cases of I.T.P., 31.4% were considered to be at least possible cases of S.L.E., and had at least one manifestation of S.L.E. other than I.T.P. If the seven cases with inadequate follow-up are excluded, the percentage of "possible" cases would be 36.4.

Incidence of S.L.E. in Combined Series: In addition to the cases listed in the previous section from the post-July, 1949, series, we are reporting two cases of definite S.L.E. (cases 9 and 10) that were first diagnosed as I.T.P. and splenectomized at other hospitals; and the pre-1949 series, four definite cases of S.L.E. (cases 11–14), and two possible cases (cases 23 and

TABLE 3

Splenectomized Cases of Idiopathic Thrombocytopenic Purpura (I.T.P.) with Manifestations of Systemic Lupus Erythematosus (S.L.E.)

Diagnostic Class	Case No.	New England Center Hospital No.	Sex	Age at Splenectomy	Year of Splenectomy	Spleen, Weight gm.	Manifestations of S.L.E. After Splenectomy for I.T.P.						Relapse, Thrombocytopenic Purpura	Exacerbation S.L.E. by Splenectomy	Antecedent Manifestations of S.L.E.	Other Manifestations of S.L.E. Cause of Death
							Spleen, Perivascular Fibrosis	L.E. Test	Arthritis	Discoid Lupus	Coombs' test	Hemolytic Anemia				
"Definite" S.L.E.	1	89-272	F	22	1954	140	4+	–	–	–	–	–	–	–	None	Hematoxylin bodies, spleen, lymph nodes
	2	49-230	F	22	1950	138	4+	na*	–	–	na	–	+	?	None	Pleuritis, pericarditis; died Staph. septicemia
	3	B.F.H. 16-601	F	13	1951	150	–	–	–	4+	–	–	–	–	? Discoid lupus	None
	4	42-408	F	18	1951	160	–	+	+	4+	+	+	+	–	? Discoid lupus	Pleuritis
	5	43-630	F	32	1949	130	–	+	+	+	–	–	–	–	None	None
	6	98-087	F	31	1956	150	4+	+	–	±	+	+	+	–	False-positive S.T.S., hyperglobulinemia	None
	7	64-934	F	21	1952	135	4+	+	+	–	–	–	–	+	Arthralgia six months	Died nephritis two years
	8	87-208	F	40	1954	90	–	–	+	4+	–	–	+	–	None	None
	9	105-925	F	23	1955	na	4+	+	+	4+	+	+	–	+	None	Hyperglobulinemia
	10	112-477	F	24	1954	na	na	+	+	+	–	–	–	–	None	None
	11	61-383	F	52	1947	130	4+	–	+	4+	–	–	+	–	Arthritis, ? discoid lupus	Died cerebral hemorrhage
	12	24-315	F	18	1947	105	4+	–	+	–	–	–	–	–	History of rheumatic fever	None
	13	L.B.	F	19	1946	na	na	–	–	4+	–	–	–	–	None	None
	14	30-735	F	73	1949	65	4+	na	–	–	na	–	–	–	None	Died 1949 of unknown cause
"Probable" S.L.E.	15	106-743	F	46	1956	150	–	±	±	–	–	–	±	–	? Rheumatic heart disease	Arthralgia
	16	63-634	F	22	1951	120	–	na	+	–	–	–	–	–	None	Raynaud's phenomenon
"Possible" S.L.E.	17	76-400	F	28	1953	150	–	–	–	±	–	–	±	–	None	None
	18	61-532	F	46	1951	110	–	–	–	–	–	–	–	–	None	Raynaud's phenomenon
	19	76-294	F	61	1953	180	–	–	±	–	–	+	–	–	Hemolytic anemia	Arthralgia
	20	72-622	F	30	1952	115	–	na	±	–	na	–	–	–	None	Arthralgia, fatigue, hypochromic anemia
	21	74-073	F	27	1953	120	–	–	±	±	–	–	–	–	None	Arthralgia
	22	43-186	F	27	1949	140	–	–	–	–	–	–	–	–	None	Urticaria, unexplained fever, fatigue, anemia
	23	24-366	F	15	1947	250	–	–	–	–	–	+	–	–	None	None
	24	16-524	F	56	1945	na	–	na	+	–	na	–	–	–	Leukopenia, arthralgia	None

* na = not available.

TABLE 4

A. Sex Incidence in I.T.P.

	"Acute" I.T.P.			No. of Cases	"Chronic" I.T.P.	
	No. of Cases	Female	% Female		Female	% Female
Hirsch[24]	18	9	50	52	33	63
Current Series	4	2	50	47	43	92
Combined Series	22	11	50%	99	76	77%

B. Sex Incidence in S.L.E.

	Cases of S.L.E.	Female	% Female
Jessar[25]	44 (his own)	43	98
	323 (from literature)	275	85
Shearn[46]	34	31	91
Dubois[13]	163	145	88.9
Harvey[23]	138	108	78
Gold[20]	26	24	92.3
Combined Series	728	626	86%

24) (table 3 and case reports). The combined total of our splenectomized cases from the pre- and post-1949 series and of the two cases diagnosed and splenectomized elsewhere (78) showed S.L.E. in the following proportions: "definite," 14; "probable," two; "possible," eight. (See also tables 5 and 6.)

TABLE 5

S.L.E. after Splenectomy for I.T.P.

	Pre-July, 1949	Post-July, 1949	Total
Cases I.T.P.	27	51	78
Follow-ups	12	44	56
"Definite" S.L.E.	4	8	12
"Probable" S.L.E.	0	2	2
"Possible" S.L.E.	2	6	8

Sex Incidence: In the post-July, 1949, series of splenectomized I.T.P., 45 of the 51 cases were females (table 4A). In the entire collection of 24 "definite," "probable" or "possible" S.L.E. cases there was not a single male.

Incidence of Periarterial Fibrosis in the Spleen: In our post-July, 1949, series of 51 consecutive cases of splenectomized I.T.P., four showed

TABLE 6

14 Cases "Definite" S.L.E. after I.T.P.

	Total	Only Manifestation
Splenic periarterial fibrosis	8	3
Discoid lupus	8	2
Positive L.E. test	6	0
Arthritis	8	—
Coombs' positive hemolytic anemia	3	—

definite periarterial fibrosis of the splenic blood vessels (7.8%). These represented half of the eight cases of "definite" S.L.E. diagnosed in this series. Of these four cases, two (cases 1 and 2) had the splenic lesion as the only manifestation of S.L.E. other than I.T.P. In the entire collection of 14 cases of "definite" S.L.E., eight had well marked periarterial fibrosis. Three of these (cases 1, 2 and 14) were diagnosed as "definite" S.L.E. solely on the basis of periarterial fibrosis plus I.T.P. In cases 6, 7, 9, 11 and 12, various other manifestations of S.L.E. appeared (table 3 and case reports).

Incidence of "Discoid" Lupus: In the collected series of 14 cases of "definite" S.L.E., three (cases 3, 4 and 11) had skin eruptions which may have been discoid lupus prior to splenectomy for I.T.P. These patients later developed lesions which were clearly discoid lupus. In case 3 this was the only feature, apart from I.T.P., for making the diagnosis of "definite" S.L.E. Cases 4 and 11, on the other hand, later developed many other evidences of S.L.E. Discoid lupus first became evident after splenectomy for I.T.P. in five other patients (cases 5, 8, 9, 10 and 13). Case 13 was the only one whose rash was the sole other manifestation of S.L.E. apart from I.T.P. Eight of the 14 collected cases thus had discoid lupus either before or after splenectomy for I.T.P., and in two of these (cases 3 and 13) there were no other manifestations of S.L.E. apart from the I.T.P.

Incidence of Positive L.E. Cell Test: Six of the 14 cases of "definite" S.L.E. developed positive L.E. tests. (For L.E. tests prior to splenectomy, see section on antecedent manifestations.) Case 15, which we have labeled as a "probable" case of S.L.E., had a weakly positive L.E. test and mild arthritis. In five patients (cases 4, 5, 6, 9 and 15) the first positive L.E. test was obtained at the examination in response to our recall letter. In cases 6, 9 and 15, previous tests had been negative. Cases 4 and 5 had had no previous L.E. tests; the diagnosis of S.L.E. was made in these as a direct result of the recall examination. In cases 6 and 9, although previous L.E. tests had been negative, the diagnosis was strongly suspected before this examination, and the positive tests were now confirmatory.

L.E. tests on the recalled splenectomized cases of I.T.P. thus yielded two previously undiagnosed cases of S.L.E. (cases 4 and 5), and confirmed the diagnosis in two suspected cases (cases 6 and 9). In case 4 this was six years after splenectomy for I.T.P., and in case 5, eight years post-splenectomy. Review of the course of these cases showed that they both had had other manifestations suggestive of S.L.E. since splenectomy, but these had not been recognized as such.

No case had a positive L.E. cell as the *only* evidence of S.L.E. other than I.T.P.

The significance of the L.E. test in the diagnosis of S.L.E. is discussed below.

Response of Thrombocytopenic Purpura to Splenectomy: In this series of 14 cases of "definite" S.L.E., five had relapse of their thrombocytopenic

purpura (35.7%). In the post-July, 1949, series of chronic I.T.P. (with the 10 cases of "definite" and "probable" S.L.E. removed), there were 12 failures or relapses in 30 cases (40%).

Exacerbation of S.L.E. by Splenectomy: Two of the 14 cases of "definite" S.L.E. (cases 7 and 9) appeared to develop acute dissemination of their S.L.E. after splenectomy. Case 7 had had some arthritis of the fingers prior to the onset of her I.T.P., but case 9 had had no antecedent manifestation in any way suggestive of S.L.E. The former died of S.L.E. two years after splenectomy, and the latter was fairly well controlled on continuous prednisone therapy.

Antecedent Manifestations of S.L.E. in 14 Definite Cases: Eight of the 14 definite cases of S.L.E. had had no evident antecedent manifestations of S.L.E. prior to the development of purpura. Three (cases 3, 4 and 11) had skin eruptions which in retrospect were probably discoid lupus. One of these (cases 11) also had evidence of rheumatoid arthritis. Case 7 had had some joint pains for six months prior to splenectomy. Case 6 had a false-positive serologic test for syphilis (*Treponema pallidum* immobilization test later was negative), and hyperglobulinemia. Case 12 had a history of rheumatic fever as a child. All 14 cases were thought to have typical I.T.P. at the time of splenectomy.

Four of the 14 cases were splenectomized before the advent of the L.E. test. Two (cases 9 and 10) had had splenectomies at other hospitals prior to their initial examination at the New England Center Hospital, and did not have L.E. tests performed prior to surgery. Of the remaining eight cases, four (cases 1, 6, 7 and 8) had L.E. tests performed before splenectomy; these tests were all negative.

Cases 15–24, diagnosed as "probable" or "possible" S.L.E., included seven cases with no antecedent manifestations. Case 15 had physical findings suggestive of rheumatic heart disease, although there was no history of rheumatic fever. Case 19 presented auto-immune hemolytic anemia, and in case 24, arthralgia and leukopenia were present.

Thus no antecedent manifestations of systemic lupus were present in 15 of the 24 cases of "definite," "probable" and "possible" S.L.E. occurring in cases diagnosed as I.T.P. prior to splenectomy, and in the other nine they were, for the most part, minimal and had gone unrecognized as such. Whether splenectomy was in some measure responsible for the ultimate development of dissemination is a legitimate subject for conjecture.

BRIEF COMMENTS ON INDIVIDUAL CASES. (See table 3 for further details.*)

A. *"Definite" S.L.E.; Post-July, 1949, Series (cases 1–8).*

Case 1. This female patient was a typical case of I.T.P. on admission. There was an excellent and sustained platelet response to splenectomy. The only evidence

* Cases 1, 7, 9, 11 and 13 are the same as cases 3, 2, 9, 4 and 1, respectively, previously reported by Dameshek.[9]

for the diagnosis of S.L.E., other than thrombocytopenic purpura itself, was in the pathology of the spleen and lymph nodes. The spleen showed marked onion-skin lesions of the arterioles, and "hematoxylin bodies" were present in both the spleen and the lymph nodes. These findings, in association with I.T.P., make the diagnosis of S.L.E. "definite."

Splenectomy did not exacerbate the S.L.E. Indeed, it apparently resulted in a "cure" of the thrombocytopenia, although since the patient has been followed for only 37 months, relapse is still possible.

Case 2. This 22 year old girl presented as a typical case of I.T.P. Splenectomy, which resulted in only a fair platelet response, was followed by a stormy postoperative course, with high fever, peritonitis, pleural effusion and pulmonary atelectasis and, later, death. The spleen showed the typical onion-skin lesions of S.L.E. The high fever and polyserositis occurring after splenectomy were thought to be due to aggravation of the lupus process, although the finding of a *Staphylococcus aureus,* coagulase positive, cultured from the peritoneum, pleura and pancreas, threw some doubt on this idea.

As in case 1, the diagnosis of S.L.E. was considered as "definite" because of the association of thrombocytopenic purpura with extensive onion-skin lesions of the spleen.

Case 3. At age 13 this girl had been admitted to the Boston Floating Hospital (a unit of the New England Medical Center) with what was considered to be typical chronic I.T.P. A skin eruption was thought to be poison ivy, although there was an associated malar and periorbital flush. Splenectomy resulted in a "cure" of the thrombocytopenia, which persisted during a six-year follow-up period. The splenic pathology was negative for S.L.E. On examination six years after splenectomy the patient presented the typical "butterfly" eruption of lupus, which had been exacerbated by exposure to the summer sun. The combination of thrombocytopenic purpura, so often a manifestation of S.L.E., and discoid lupus makes this a "definite" case of S.L.E. (See discussion of discoid lupus as criterion of "definite" S.L.E.) Splenectomy did not appear to accelerate the course of the S.L.E.

Case 4. At age seven this girl first developed a severe generalized skin eruption, which was considered to be due to moniliasis and which had persisted for 16 years. At age 16, nine years after the onset of rash, she developed thrombocytopenic purpura. Splenectomy was performed but the platelets responded only after a course of ACTH therapy. The splenic pathology added neither to the diagnosis of S.L.E. nor generalized moniliasis. There was a remission of purpura for four years, followed by a clear-cut relapse. The platelets were thereafter maintained with continuous prednisone therapy, although only small doses (10 mg. daily) were required. Further symptoms of S.L.E. did not appear until 1956, 15 years after the onset of the skin disease. These consisted of pleurisy, unexplained fever, migratory polyarthritis, appearance of an apical diastolic murmur, Coombs-positive hemolytic anemia, and a strongly positive L.E. cell test in June, 1957.

It is possible that the rash was basically lupus from its onset, with monilia a secondary invader. At the time of writing, much of the appearance of discoid lupus was present. Thus it seems likely that this patient had had S.L.E. for 16 of her 23 years. This clearly is a "definite" case of S.L.E., where splenectomy did not appear to accelerate the S.L.E., but seemed merely an incident in the course of the disease.

Case 5. At age 32, splenectomy had been performed on this woman for typical "chronic I.T.P." There was an excellent and sustained response of the thrombocytes (eight-year follow-up). Four or five years after splenectomy, discoid lupus appeared. About seven years postsplenectomy, migratory arthritis involving chiefly the fingers, shoulders and cervical spine began. Eight years postsplenectomy a positive L.E. cell test was found during recall examination. The sequence of I.T.P.,

discoid lupus, arthritis and a positive L.E. test makes the diagnosis of S.L.E. definite. Splenectomy did not appear to accelerate the course of the S.L.E. in this case.

Case 6. Although this female patient presented with thrombocytopenic purpura, there was a suspicion of S.L.E. from the start because of a positive Hinton test for syphilis (the *Treponema pallidum* immobilization test was later found to be negative), a 1 plus positive Coombs' test, and a moderate increase in the serum globulins. The L.E. tests, however, were negative. The platelet count responded well to prednisone, but was not maintained when the drug was withdrawn. Splenectomy was performed, although today, with our greater experience in the treatment of I.T.P. with prednisone,[45] we know that it is usually possible to maintain the platelets at reasonably normal or somewhat low levels on very small doses of prednisone for indefinite periods. It is therefore quite likely that the platelets could have been maintained at reasonably good levels with small doses of prednisone indefinitely, thus avoiding the operation of splenectomy. At any rate, the thrombocytopenia recurred four months after splenectomy, and prednisone was then required to maintain the platelet level. The removed spleen showed extensive periarteriolar fibrosis.

Splenectomy did not appear to accelerate the course of the disease. At the recall examination, the L.E. test was weakly positive, i.e., four typical L.E. cells were found after a two-hour search.

The association, in this case, of thrombocytopenic purpura, positive Coombs' test, onion-skin lesions in the spleen, false-positive serologic test for syphilis, hyperglobulinemia and a positive L.E. cell test made the diagnosis of S.L.E. quite certain.

*Case 7.** This case was considered to be one of I.T.P., although the question of S.L.E. was aroused by some suggestive symptoms. For six months the patient had complained of some stiffness and limited motion of the finer finger joints, especially in the mornings. Two months prior to admission she had developed a short bout of unexplained fever, and the blood sedimentation rate was rapid. The L.E. test, however, was negative. Splenectomy resulted in a "cure" of the "I.T.P.," but within a few months the patient became severely ill with pleurisy, pericarditis, arthritis and renal disease. The L.E. test was strongly positive at this time. The spleen showed extensive perivascular changes of the "onion-skin" type.

Two years after splenectomy the patient died of renal disease.

Case 8. This 40 year old woman presented as a typical case of chronic I.T.P. which responded well at first to splenectomy. The L.E. test was again negative, and the spleen failed to show evidence of S.L.E. One year postsplenectomy a relapse of the thrombocytopenic purpura occurred. This was controlled with small doses of prednisone (10 mg. daily). At this time the patient also developed arthritis, with swelling of the knees and spindling of the fingers. About two years after splenectomy following exposure to a sunlamp, a butterfly rash of the face developed. Repeat L.E. test at this time was again negative.

I.T.P., and subsequent arthritis and discoid lupus, make this a "definite" case of S.L.E., even in the absence of a positive L.E. test. Splenectomy did not appear to have an immediate accelerating effect on the course of the disease.

B. *"Definite" S.L.E. after I.T.P.; First Treated at Other Hospitals (Cases 9 and 10).*

Case 9. This 23 year old female was treated for typical I.T.P.; splenectomy had been performed at the Soldier's Home, Holyoke, Massachusetts. The spleen showed extensive onion-skin lesions. Surgery was followed by the onset of migratory polyarthritis. The purpura responded to splenectomy, but the patient developed severe

* This case has been reported in detail.[8]

anemia. There was much difficulty in cross-matching blood for transfusion. At this time the patient was transferred to the New England Center Hospital, where she was found to have a severe auto-immune hemolytic anemia. The L.E. test was constantly negative and the Coombs' test was positive. There was an excellent response to prednisone therapy. At recall examination, on September 5, 1957, typical discoid lupus lesions of the arms were noted; these had occurred following sun exposure the week before. The Coombs' test was still strongly positive, there was moderate hyperglobulinemia, and a positive L.E. test was found for the first time.

The association of thrombocytopenic purpura, onion-skin lesions in the spleen, migratory arthritis, a Coombs'-positive hemolytic anemia, hyperglobulinemia, discoid lupus and, finally, a strongly positive L.E. cell test make this a definite case of S.L.E. The disease had been kept under control with prednisone. In this instance there appears to have been an acceleration of the course of the S.L.E. by splenectomy.

*Case 10.** This 28 year old Puerto Rican female was admitted to the New England Center Hospital for reëvaluation in May, 1957. Four years previously she had developed typical I.T.P. during a pregnancy. Splenectomy in Puerto Rico had resulted in a "cure" of the thrombocytopenia. Two years later she developed discoid lupus, and this was followed a year later by migratory polyarthritis. The L.E. test was strongly positive. At her most recent hospitalization she appeared to be well, but a grade III systolic murmur was present, there were some skin atrophy over the cheeks and suggestive spindling of the fingers, and the liver edge was just palpable. The L.E. test was strongly positive.

The sequence of thrombocytopenic purpura, discoid lupus, migratory arthritis with some finger joint spindling, a heart murmur and strongly positive L.E. tests makes this a "definite" case of S.L.E.

C. *"Definite" S.L.E. after I.T.P.; Pre-July, 1949 Series (Cases 11–14).*

Case 11. At age 52 splenectomy had been performed on this woman at the New England Center Hospital in 1947 for I.T.P. For five years prior to the onset of purpura she had had arthritis of the hands and feet, and a butterfly rash over the bridge of the nose and the cheeks. The rash was typical discoid lupus, and x-rays of the hands and right elbow showed changes consistent with rheumatoid arthritis. The spleen showed the onion-skin lesions of S.L.E. The platelets rose slowly after splenectomy; eventually they were sustained at levels between 250,000 and 300,000 without overt purpura. The patient died at another hospital of a cerebral hemorrhage in 1957.

S.L.E. could be diagnosed in this case prior to the onset of I.T.P. on the basis of the combination of discoid lupus and arthritis. The diagnosis certainly would be made today, even though the disease was relatively slow in its development, and "discoid" lupus seemed to be in the forefront. In 1947, however, the patient arrived on the hematology service as a case of "I.T.P." The L.E. test was never positive.

Case 12. At age 18, splenectomy had been performed on this woman at the New England Center Hospital in 1947 for chronic I.T.P. A good sustained platelet response occurred after splenectomy, with no sign of relapse after 10 years. The spleen showed the characteristic onion-skin lesions of S.L.E. The past history included attacks of rheumatic fever at ages seven and 10. The patient had had an episode of painful swelling of several finger joints and of the right big toe in 1955. In the summer of 1956 there was an unexplained fever lasting almost two months. There had been no other symptoms. The L.E. test was negative.

* We are indebted to Dr. Enrique Perez, Santurce, Puerto Rico, for his summary of the past history of this patient.

I.T.P., splenic perivascular fibrosis, a history of rheumatic fever, recent arthritis and prolonged fever make the diagnosis of S.L.E. definite. It is possible that the actual onset of S.L.E. should be dated back to the patient's initial attack of rheumatic fever, about 10 years prior to the onset of her I.T.P.

Case 13. At age 19, splenectomy had been performed on this woman for I.T.P. on July 13, 1946. The spleen was stated to be negative for S.L.E. changes. Platelet response was excellent and was sustained for 11 years. In the summer of 1949 an eruption of the face was first noted. On examination in May, 1956, the rash was found to be characteristic of chronic discoid lupus. The eruption was well controlled with small doses of prednisone.

This is a "definite" case of S.L.E. because of the combination of I.T.P. and discoid lupus.

Case 14. This 73 year old woman was first admitted to the New England Center Hospital in September, 1948, because of numerous petechiae and ecchymoses, with mucous membrane and gastrointestinal bleeding. There was a history of easy bruising for 25 years. The platelet count was 23,000. Expectant therapy with blood transfusions led to a spontaneous remission, with the platelet count returning to normal in two weeks. Seven months later the patient was re-admitted because of a recurrence of purpura and thrombocytopenia. Splenectomy produced a good platelet response. The postoperative course was complicated by myocardial infarction on the second day, followed by a cerebral embolus on the sixth day. Recovery then was uneventful, but death occurred elsewhere four months later of unknown cause.

The spleen showed extensive perivascular fibrosis consistent with S.L.E.

This patient very likely had had chronic relapsing I.T.P. for 25 years. The combination of I.T.P. and extensive splenic perivascular fibrosis fulfills the criteria for a diagnosis of "definite" S.L.E. We are somewhat hesitant in accepting this, however, because of the patient's age and the possibility that the splenic lesions were nonspecific, possibly due to arteriosclerosis. The probability that I.T.P. had been present for many years perhaps overrules this objection. This pre-1949 case might have been more satisfying if the history, examination and laboratory tests had been performed in accordance with more recent knowledge of I.T.P. and S.L.E. Thus, while fulfilling the criteria for "definite" S.L.E., this case is presented with reservations. Since it is in the pre-1949 series, it does not affect the percentages in our major incidence figures.

"Probable" S.L.E.; Post-July, 1949 Series (Cases 15 and 16).

Case 15. This 46 year old woman presented as a typical case of I.T.P. She was treated with prednisone in high dosage but failed to respond. There was a fairly good response to splenectomy, although she had continued to show some bleeding tendency. No further corticosteroid therapy, however, has thus far been necessary.

Arthralgia and slight spindling of the fingers appeared following splenectomy. In addition, the most recent L.E. test was weakly positive, i.e., four typical L.E. cells were seen after a two-hour search. There is strong indication that the patient has S.L.E., although a diagnosis of "definite" S.L.E. cannot be made, pending repetition of the L.E. cell test or the appearance of other manifestations.

Case 16. A patient with typical chronic I.T.P. which responded to splenectomy had shown no sign of relapse of her thrombocytopenia during a 64-month follow-up. She had, however, developed migratory polyarthritis and Raynaud's syndrome. The combination of thrombocytopenic purpura, polyarthritis and Raynaud's syndrome is perhaps sufficient to call this a definite case of S.L.E. Since, however, the patient has not been followed at first-hand, we will consider her a probable case, at least until the evidence becomes a little stronger.

"Possible" S.L.E.

A. *Post-July, 1949 Series (Cases 17–22).*

Case 17. On April 9, 1953, splenectomy had been performed on this woman at age 28 for chronic I.T.P., with good response. The platelets later fell to a level of about 200,000 (normal, 500,000), but there was no bleeding tendency. Two children since splenectomy both had neonatal purpura. The most recent platelet count (July, 1957) was 516,000. Some telangiectasia over the left cheek was first noted in 1953. On reëxamination in 1957 this was markedly increased and strongly suggestive of discoid lupus. This was thought to point to the ultimate development of other features of systemic lupus, and thus to a possible case of the disease.

Case 18. Splenectomy had been performed on this woman in August, 1951, at age 46, for chronic I.T.P., with a good and sustained platelet response. The platelets reached a level of 2,000,000 in the first postoperative week. This was associated with the development of phlebothrombosis, which was treated with anticoagulant. At the last visit (July 1, 1957), the platelets were 850,000. The patient complained that in damp, cold weather the hands became white and painful. She wore two or three pairs of gloves in winter. Thus, on examination the patient appeared to have the manifestations of Raynaud's phenomenon, which occasionally occurs as an early manifestation of S.L.E.

Case 19. Splenectomy was performed on April 9, 1953, on this woman at age 61 for I.T.P. and hemolytic anemia. There had been an excellent and sustained response. At the last examination (July 1, 1957), she was well, and no underlying cause for the "Evans' syndrome" had manifested itself. She suffered occasionally from stiffness of her shoulders, not unusual at her age. The occurrence of Evans' syndrome (thrombocytopenic purpura and hemolytic anemia) always raises the strong suspicion of underlying S.L.E.

Case 20. On November 5, 1952, splenectomy had been performed on this woman at age 30 for chronic I.T.P. There was a good and sustained platelet response. At the last visit (August, 1956), she complained of recurrent joint pains, involving particularly the left knee, and of easy fatigability. Examination was normal except for a mild hypochromic anemia (hemoglobin, 10.5 gm.; red blood cells, 4,200,000). In the presence of previous I.T.P., these symptoms are sufficient to arouse suspicion of an underlying S.L.E.

Case 21. In January, 1953, splenectomy had been performed on this woman at age 27, with a good and sustained platelet response. At her last visit (August 9, 1957), she was noted to have definite telangiectasia over the cheeks. She stated that she had been having an intermittent eruption of the left side of the face, consisting of "small red bumps". She had been having pain in her fingers for two years, but had noted no swelling. The suggestion of possible discoid lupus, and arthralgias of the fingers following thrombocytopenic purpura raise a strong suspicion of S.L.E.

Case 22. In August, 1949, splenectomy had been performed on this woman at age 27 for I.T.P., with a good and sustained platelet response. No evidence of relapse of thrombocytopenia was present after an eight-year follow-up. Suspicions of S.L.E. are raised on the rather tenuous grounds that she had been having attacks of "hives" since 1949, that a rash of the face had occurred in the summer of 1957 (said to be poison ivy), that she ran periodically very low grade, unexplained afternoon temperature elevations, and that she had suffered from easy fatigability and mild anemia.

B. *Pre-July, 1949 Series (Cases 23 and 24).*

Case 23. This 15 year old female had had a splenectomy on December 16, 1947, for thrombocytopenic purpura and auto-immune hemolytic anemia, with an excellent

response of both conditions. The spleen weighed 250 gm., and the pathology was consistent with I.T.P. and hemolytic anemia. At recall examination (July 5, 1957), her blood and platelet counts were normal. Reticulocytes were 0.7%; total bilirubin, 0.7%. Coombs' test, L.E. cell test and Hinton test were negative. This is considered as a possible case in view of the combined hemolytic and thrombocytopenic abnormalities ("Evans' syndrome").

Case 24. A 55 year old female had splenectomy performed in September, 1945, for I.T.P. There had been leukopenia and recurrent episodes of migratory polyarthritis for two years. Hysterectomy had been performed in 1938 for bleeding (the platelet count is not known). Platelet and white blood counts responded well to splenectomy and remained at normal levels four years later, at the last examination.

The combination of thrombocytopenia, leukopenia and migratory arthritis is suggestive of S.L.E. A recent examination for additional evidence of S.L.E. is, unfortunately, not available.

Discussion

1. *Periarterial Fibrosis in the Spleen as a "Diagnostic" Criterion of "Definite" S.L.E.* We have accepted well marked periarterial fibrosis in the spleen of patients with I.T.P. as a "diagnostic" criterion of "definite" S.L.E. The matter of specificity of periarterial fibrosis in the spleen has been investigated by several authors.[30, 27, 31, 17, 47, 48] "Onion-skin" lesions of the spleen, first described in detail by Klemperer et al.[30] in 1941, are now generally regarded as pathognomonic of S.L.E. Eversole[17] affirms that present information strongly supports the view that the lesion, when "well marked," is pathognomonic of the disease. He points out that well defined lesions of this type have never been found in any condition other than S.L.E., or in any case where the clinical and pathologic findings were incompatible with S.L.E.

Klemperer[31] reported positive findings in 19 of 20 cases of S.L.E. Kaiser[27] found the characteristic lesions in 15 of 18 cases of S.L.E. In 22 of 970 consecutive autopsies he found some periarterial fibrosis (2.3%), but in no instance were the lesions as extensive, in either size or distribution, as in S.L.E. In four of 13 cases of I.T.P. (30.8%), he found extensive lesions. This was statistically significant when compared to the control series. The clinical histories of these four patients were reviewed and none of the usual features of S.L.E. was found. Kaiser concluded that in the present state of knowledge (1942), "onion-skin" lesions in the spleen were highly suggestive of S.L.E. but could not be considered to be pathognomonic, regardless of their extent, in any given case. It is of interest to note that Eversole,[17] upon reviewing one of Kaiser's four cases of I.T.P. with periarterial fibrosis, found typical wire-loop lesions in the kidneys. Fifteen years after Kaiser's study it has become increasingly apparent that I.T.P. is often merely a part of the larger syndrome of S.L.E.

Teilum[48] has questioned the specificity of the periarterial fibrosis lesion because it has been found in patients suffering from acute rheumatic fever as well as in I.T.P. However, syndromes indistinguishable from rheumatic fever do occur in S.L.E.[28] and may be part of the larger syndrome.

Harvey [23] reports that Rich reviewed cases at the Johns Hopkins Hospital in whom a clinical diagnosis of I.T.P. had been made, and whose spleens were available for microscopic examination. In six cases periarterial fibrosis was noted. Two of these later developed clinical evidence of S.L.E. more than two years after splenectomy. One other patient, not suspected clinically of having S.L.E., had visceral lesions of the disease at autopsy. Rich believes that pronounced periarterial fibrosis of the spleen rarely, if ever, occurs in conditions other than S.L.E.

Eversole,[17] in a similar study, has reported six such cases. It is not clear whether these are the same cases described by Rich; however, four of them were reported by Harvey.[23] Of the two not previously reported, one had no antecedent symptoms of S.L.E., and the periarterial fibrosis in the spleen was the only evidence, apart from I.T.P., of S.L.E. The other patient was an 11 year old Negro girl who had been treated for a positive Wassermann test, and had had joint pains prior to the onset of her thrombocytopenic purpura. She developed rheumatoid arthritis two years after splenectomy.

2. *The L.E. Test as a "Diagnostic" Criterion of "Definite" S.L.E.* Positive L.E. tests have occurred with reactions to certain drugs, and in other circumstances which do not appear to be compatible with S.L.E.[15, 42, 52, 37] Like all laboratory tests, the L.E. test is subject to error.[32] It has been our experience that, properly performed, it is quite reliable. We have not seen a clearly positive L.E. cell test in any patient who has not had other manifestations consistent with S.L.E., although others [38] have reported this to occur. We would certainly accept as "definite" S.L.E. a case of I.T.P. with a positive L.E. test as the only other manifestation of the disease. In our series, however, there is no case of I.T.P. with a positive L.E. test as the only other evidence of systemic lupus erythematosus to be found. The late development of positive L.E. tests in cases 4 and 5, six and eight years, respectively, after splenectomy, suggests the desirability of prolonged follow-up in such cases of I.T.P.

3. *Discoid Lupus as a "Diagnostic" Criterion of "Definite" S.L.E.* Kaposi [28] in 1872 noted that patients with skin lupus sometimes developed systemic disease and died. In recent years, opinion has crystallized to support the view that discoid lupus is very often simply a phase of the systemic disease.[51, 47, 10, 13, 53, 35, 43, 33, 5, 23] Reiches [43] suggests that clinically the lupus erythematosus syndrome may be divided into: (1) a localized, discoid (cutaneous) phase which is generally benign; and (2) a systemic (disseminated) phase which may or may not be associated with skin lesions. It is apparent that the discoid phase, when existing alone, often merges into the systemic phase of lupus erythematosus.

Marten [33] found that more than half of a series of 66 cases of discoid lupus had associated hematologic or clinical signs and symptoms pointing toward the systemic disease. In Wilson's series,[53] 26% of "subacute"

S.L.E. and 20% of "acute" S.L.E. were preceded by chronic discoid skin lesions. Montgomery and McCreight [35] found that chronic discoid lesions preceded "subacute" and "acute" S.L.E. in 22% of their cases. Harvey [23] concluded that the evidence was impressive that chronic discoid lupus may evolve into the acute systemic form. Dubois [10, 13] unequivocally accepts discoid lupus as a symptom of systemic lupus. It is apparent that discoid lupus may sooner or later become systemic lupus, and that the latter varies a great deal in the rapidity of its course. Many cases of the systemic disease are certainly far more indolent in their development than was previously thought to be the case. Perhaps it might be well to categorize lupus erythematosus in all forms as acute, subacute or chronic, rather than to draw any clear distinction between the discoid and disseminated forms.

We feel that we are on very firm ground when we consider a case to be "definite" S.L.E. that has discoid lupus and I.T.P., a fairly common manifestation of S.L.E. It is evident from our studies that "discoid" lupus is simply a dermatologic manifestation of the generalized vasculitis of the disease, and that it may either precede or follow the onset of I.T.P. or the other manifestations of S.L.E.

Response of Thrombocytopenia in S.L.E. to Splenectomy: Harvey [23] stated that splenectomy in S.L.E. is usually followed by a sustained rise of the platelet count. In his collected series, 15 cases had splenectomy performed, with one delayed "response" for three months (which we would consider a failure of splenectomy; the response, a spontaneous remission), and one relapse after seven years. In our series of 14 "definite" cases of S.L.E. following I.T.P., five (35.7%) had a relapse of their thrombocytopenia. This approximates the usual figures for relapse in I.T.P.[24] It is our impression, therefore, that the chance of failure or relapse after splenectomy in this group of cases is as great as in I.T.P. in general.

Exacerbation of S.L.E. by Splenectomy: "Exacerbation" of S.L.E. by splenectomy has been described. Dameshek and Reeves [8] reported three patients in whom this occurred, one with I.T.P. (case 7 of this paper), and two with a Coombs'-positive hemolytic anemia. Hargraves [21, 22] mentions three cases who had splenectomies for "hypersplenism"; thrombocytopenia was a feature in two and neutropenia in one. Acute S.L.E. became prominent in all three shortly after recovery from the original condition. One of the three patients was a girl, age 14, who died with typical features of S.L.E. 10 months postsplenectomy. The L.E. cell test was negative before splenectomy and became positive after. The other two patients, with similar stories, were still alive.

Dr. Maurice J. Costello, of New York, in his discussion of Montgomery's paper,[35] describes a case of this type and quotes Dr. George Baehr as saying that he had seen three cases of acute lupus erythematosus of the disseminate type following splenectomy for thrombocytopenic purpura.

If exacerbation is the result of removal of a splenic inhibiting factor, as

one of us has suggested,[9] this inhibition does not seem to be very effective in most cases. It is of course possible that splenectomy in those instances where exacerbation has seemed to occur was merely an incident in the course of the disease, and that exacerbation would have occurred without splenectomy. The sequence of events in these cases has, however, been so striking that we feel that a causal relationship is probable, and that splenectomy in S.L.E. carries a potential risk of future dissemination. This would apply also to splenectomy for I.T.P., in view of the real possibility, as shown by our incidence figures, that any given case may have an underlying S.L.E.

We are, to a large extent, avoiding the issue of exacerbation in our current practice, since we are now performing splenectomy only in those cases of I.T.P. and auto-immune hemolytic anemia that do not respond to prolonged prednisone therapy.[45] The possibility of exacerbation of S.L.E. is an additional reason for the use of steroids rather than splenectomy in these cases.

It will be several years before it will be possible to evaluate the results of cases of I.T.P. treated with prednisone and without splenectomy. Whether the incidence of S.L.E. in these cases will be as great as in those splenectomized will be of interest. Prednisone may well submerge the symptoms of S.L.E., whereas splenectomy may bring them out.

Predominance of Females in I.T.P. and S.L.E.: About six out of seven cases of S.L.E. occur in females (table 4B).

In I.T.P. there also is predominance of females, at least among the "chronic" cases (table 4A). In our combined series, 77% of 99 "chronic" cases of I.T.P. were female. "Acute" I.T.P., often associated with an acute infectious disease or a drug, seems to behave differently from "chronic" I.T.P. This type of case does not appear to be associated with S.L.E. In many instances, however, the distinction between "acute" and "chronic" I.T.P. is not sharp. The high incidence of chronic I.T.P. in females parallels its high incidence in S.L.E. Since the 78 cases of splenectomized I.T.P. included in this study consisted of 69 females and only nine males, it is not too surprising that none of our cases of "definite," "probable" and "possible" S.L.E. is a male. Of Harvey's [23] collected 22 cases, three are males; all of these had some antecedent manifestations of S.L.E. before the onset of thrombocytopenic purpura. Gold [20] has reported two cases (not included in Harvey's collection) of I.T.P. where S.L.E. later became evident. One of these was a male who had a splenectomy with a good platelet response, but later developed discoid lupus, intermittent fever, joint symptoms and fundus lesions. The sequence of I.T.P. followed by manifest S.L.E. thus does in rare instances occur in males. One of us [9] has suggested that there may be some etiologic significance in this preponderance of females in S.L.E. and I.T.P., and the frequent coexistence of the two. This is related to the menstrual cycle. In menstruation the basic materials needed—

blood cells and endothelium—are shed each month in an environment of open blood vessels. Some of these altered tissues are perhaps absorbed into the circulation, to become antigens in an auto-immune process, especially in potent antibody producers.

The role of hypersensitivity in S.L.E. was considered by Fox [18] in 1943. He reported a case of S.L.E. following the administration of tetanus antitoxin, noted similarities between serum sickness and S.L.E., and wondered if S.L.E. might be an immunologic disease. Beck [2] has reviewed the evidence of hypersensitivity in the pathogenesis of S.L.E. He feels that the rise in incidence of S.L.E. is greater than that due to better diagnosis alone, and is the result of increased use of the highly antigenic potent new antirheumatic, antihypertensive, analgesic and antibiotic drugs. Positive L.E. cell tests have been obtained after reactions to such drugs as hydralazine,[15, 42] penicillin [52] and phenylbutazone.[37] These, perhaps, act either as haptens, to increase the antigenic potential of the organisms' own tissues, or to alter a tissue so that the organism fails to recognize it as its own.[3b]

The recent experimental production and demonstration of auto-antibodies to thyroid tissue in rabbits by Witebsky et al.[54, 55] have given the concept of "auto-immune disease" increased stature and an experimental basis. It gives a firmer foundation to Dameshek's [9] view that the various hematologic and vascular manifestations of S.L.E. are all due to auto-immunization, with the development of various types of auto-antibodies.

Summary and Conclusions

1. In a series of 51 consecutive cases of I.T.P. splenectomized since July, 1949, review and recall examination yielded eight "definite," two "probable" and six "possible" cases of S.L.E. Thus at least 31.4% had manifestations of S.L.E. other than thrombocytopenic purpura, and 15.7% were considered to have "definite" S.L.E.

2. Although follow-up was limited in 27 cases of I.T.P. splenectomized before July, 1949, four "definite" and two "possible" cases of S.L.E. were found. Thus 14.8% had "definite" S.L.E., and at least 22% had some evidence of S.L.E. other than thrombocytopenic purpura. More complete follow-up would undoubtedly have yielded a higher incidence. These figures are nevertheless high enough that they do not detract from the significance of the post-July, 1949, percentages, but rather tend to substantiate them.

3. Two additional cases are presented of "definite" S.L.E. developing after splenectomy for I.T.P., but diagnosed and operated upon before appearing on our service.

4. Our accumulated series of cases of S.L.E. developing after splenectomy for "I.T.P." in 78 cases was: "definite" S.L.E., 14; "probable" S.L.E., two; "possible" S.L.E., eight.

5. The criteria for diagnosis of "definite," "probable" and "possible" S.L.E. are discussed. The basis for considering periarterial fibrosis in the

spleen, discoid lupus and positive L.E. cell tests as criteria for "definite" S.L.E. in splenectomized cases of "I.T.P." is reviewed.

6. Failure of response and relapse of thrombocytopenia after splenectomy (35.7%) appear to be of the same frequency in these cases as in I.T.P. in general.

7. Exacerbation of S.L.E. occurred in two of the 14 "definite" cases after splenectomy.

8. The development of S.L.E. in cases of I.T.P. treated with prednisone and without splenectomy has not been studied because sufficient time has not yet elapsed. Perhaps the drug will submerge the manifestations of S.L.E.

9. The preponderance of females is noted, and possible etiologic implications are mentioned.

10. Its high incidence in this series indicates the need for considering S.L.E. in every case of I.T.P. Long-term follow-up is essential, since overt S.L.E. may not become evident for years after the onset of I.T.P.

Appendix

Case Reports in More Detailed Form

"Definite" S.L.E. (Cases 1–14):

Cases 1, 7, 9, 11 and 13, which have been previously reported in detail[8, 9] (see footnote above), are not repeated. Cases 2, 3 and 14, where the diagnosis of "definite" S.L.E. was based on the combination of I.T.P. and either splenic perivascular fibrosis or discoid lupus alone, have been adequately described in the section on *Brief Comments on Individual Cases* and are omitted here.

Case 4. This white female patient, born December 17, 1934, has had nine admissions to the New England Center Hospital. Her first two admissions, in July and September, 1949, were for diagnosis of a severe, generalized skin eruption of eight years' duration, which involved especially her neck, ears and fingers. Cultures from these lesions were positive for *Candida albicans*. She was considered to have moniliasis, probably systemic. At this time her blood studies showed: hemoglobin, 10.5 gm. per 100 c.c.; red blood cell count, 3.7 million per cubic millimeter; white blood cell count, 6,000 per cubic millimeter; neutrophils, 69%; lymphocytes, 23%; monocytes, 5%; eosinophils, 2%; basophils, 1%. Platelet counts were not done during these admissions, but the platelets in various smears were reported as: normal in number, three times; slightly decreased, twice; and decreased, twice.

A year later the patient began to have purpura. She was admitted in July and again in August, 1950, for study. Her rash persisted. The spleen was found to be palpable, but this was attributed to her moniliasis. Her platelet counts ranged from "none seen" to 10,000. Tourniquet test was positive. The bleeding time was 15 minutes, and the coagulation time, 7½ minutes. The bone marrow aspirate showed increased numbers of megakaryocytes, which were nongranular and did not appear to be producing platelets.

Splenectomy was performed during the patient's fifth admission, on March 17, 1951. There was no platelet response for three days postsplenectomy. ACTH was therefore started, in a dosage of 25 mg. four times a day. Her platelets rose promptly,

reaching 367,000 in two days. A peak of 834,000 was attained in a week. ACTH was discontinued after 17 days.

The spleen weighed 160 gm., and showed changes consistent with I.T.P., namely, leukocytosis with moderate eosinophilia. There was no evidence of moniliasis or S.L.E.

The patient had two admissions (August, 1953, and September, 1954), for therapy of her skin eruption, which involved practically her whole body surface area. Biopsy of her skin on September 21, 1954, was reported to show "chronic dermatitis, nonspecific, but entirely in keeping with a fungus (monilia) infection. Organism not demonstrated by specific stains." Empiric therapy with atabrine and chloroquine for the period between these admissions had seemed to improve her skin somewhat. This therapy, however, was not given with lupus in mind. Platelet count on September 19, 1954, was 598,000.

On March 28, 1956, the patient was admitted for the eighth time because of menorrhagia, bleeding gums and anemia. Since her splenectomy there had been no bleeding symptoms except for easy bruising.

Two months prior to this admission the patient had had an attack of pleurisy and fever. For the last several months there had been intermittent painful swelling of the fingers.

Physical Examination: The generalized rash continued. The liver was palpable three fingerbreadths below the costal margin. An apical diastolic murmur was heard for the first time.

The platelet count had fallen to a low of 20,000. Blood studies showed: hemoglobin, 7.2 gm. per 100 c.c.; red blood cell count 2.5 million per cubic millimeter; white blood cell count, 11,800 per cubic millimeter; neutrophils, 52%; lymphocytes, 38%; monocytes, 2%; eosinophils, 8%. The Coombs' test was positive. Thymol turbidity, 4.6; bromsulfalein, 8% retention.

The platelet count rose spontaneously to 513,000 when the menstrual period ceased. The patient was discharged from the hospital on April 4, 1956.

She was re-admitted to the hospital a few days later (April 10, 1956) because of epistaxis for one day and bleeding gums. The platelet count had fallen to 9,900. Prednisone therapy was instituted, with prompt response of the platelets. A level of 513,000 was reached on April 17, 1956. Prednisone has been administered continuously since then. It has been possible to maintain the platelets at high levels on small doses. Since September, 1956, she has been receiving only 10 mg. per day.

In response to our letter of recall, the patient was reëxamined on June 27, 1957. She was free of purpura, although there was some bleeding from the gums with tooth brushing. There had been intermittent pain and swelling of various joints, especially the fingers, wrists and knees. These symptoms had been less severe since prednisone was started. Aspirin relieved the residual symptoms. She has been subject to attacks of chills and low grade fever (100 to 101° F.) several times a year. These attacks have occasionally been associated with "pleurisy" (some chest pain on deep breathing). The major physical finding continued to be the skin eruption. This involved particularly the exposed areas, and consisted of erythema, scaling, loss of skin elasticity, telangiectasia and skin atrophy. The finger nails were severely deformed. She felt, however, that her skin was in as good condition as it had ever been. Blood showed: hemoglobin, 9.2 gm. per 100 c.c.; red blood cell count, 3.8 million per cubic millimeter; while blood cell count, 12,350 per cubic millimeter; neutrophils, 74%; lymphocytes, 13%; basophils, 4%; eosinophils, 9%; platelets, 395,000; Coombs' test, positive; L.E. cell test, strongly positive.

Case 5. This white female patient was admitted to the New England Center Hospital on September 1, 1949, at age 32, with a history of easy bruising, petechiae, and menorrhagia for three years. On admission she had numerous petechiae,

especially on her legs. Except for the spleen, which was just palpable, the remainder of the physical examination was normal. The blood studies showed: hemoglobin, 11.7 gm. per 100 c.c.; red blood cells, 4.34 million per cubic millimeter; hematocrit, 37%; white blood cells, 9,450 per cubic millimeter; neutrophils, 71%; lymphocytes, 21%; monocytes, 5%; eosinophils, 3%; reticulocytes, 1.4%; platelets, 138,000. The bone marrow aspiration showed increased numbers of megakaryocytes, which were nongranular and did not appear to be producing platelets. There was a positive tourniquet test; bleeding time (Duke), 9½ minutes; clotting time, 11 minutes; clot retraction was poor after 12 hours. Total protein, 7.7; albumin, 4.2, and globulin, 3.5 gm.%.

After two months' observations, during which time the platelets fluctuated between 57,000 and 123,000, and purpura continued, splenectomy was performed on November 9, 1949, with a prompt rise of the platelets. They reached a level of 705,000 on November 16, 1949, at the time of the patient's discharge from the hospital.

The spleen weighed 130 gm., and its pathology was consistent with I.T.P. There was no periarterial fibrosis.

The patient remained well until September, 1953, when she was re-admitted for cholecystectomy for cholelithiasis and cholecystitis. The surgical course was uneventful. At this time the blood count showed: hemoglobin, 13.2 gm. per 100 c.c.; white blood cells, 10,200 per cubic millimeter; neutrophils, 54%; lymphocytes, 29%; monocytes, 9%; eosinophils, 8%, with 582,000 platelets, which appeared to be normal on the smear.

We did not see the patient again until she was recalled in July, 1957. She had been free of purpura, but in the last three or four years had developed a skin eruption on the cheeks, forehead, chest and back, which worsened in the summer. On examination, this rash appeared to be chronic discoid lupus.

In 1956 migratory joint pains began which involved chiefly the shoulders, neck and fingers. In December, 1956, the cervical arthritis became quite severe, and the patient's physicians prescribed prednisone, which gave relief. The pain, however, recurred when the drug was discontinued.

At the patient's recall visit on July 23, 1957 she was still complaining of cervical pain. The blood studies showed: hemoglobin, 11.5 gm. per 100 c.c., red blood cells, 3.47 million per cubic millimeter; white blood cells, 8,420 per cubic millimeter; neutrophils, 52%; bands, 3%; lymphocytes, 41%; monocytes, 2%; eosinophils, 1%; basophils, 1%; reticulocytes, 0.5%; platelets, 866,000. Coombs' test was negative. The L.E. cell test showed six characteristic L.E. cells in a two-hour search. On repeat L.E. test, on August 2, 1957, 10 typical L.E. cells were found after a two-hour search.

Case 6. This white female housewife was first admitted to the New England Center Hospital on July 25, 1955, at age 40, because of purpura of four weeks' duration and severe menorrhagia with the last two periods. The current menstrual period had continued for two weeks and had been so profuse that four transfusions had been given. The past history was remarkable in the following respects: (1) she had had "dizzy spells" with tinnitus lasting for from 12 to 18 hours about every six months for seven years, since a pregnancy during which she had been "very nervous"; (2) 14 months before admission she had had an episode of sudden weakness and clumsiness of her right arm, with some motor aphasia. The latter episode had cleared slowly over a period of four months. Family history showed that her mother had died at age 42 of a cerebrovascular accident.

On admission, numerous ecchymoses were present, especially over pressure points and at the sites of injections, and there were scattered petechiae on the arms and legs. There was profuse bleeding from the cervix. The spleen was not felt. The remainder of the examination was normal.

Laboratory studies showed: hemoglobin, 9.3 gm. per 100 c.c.; red blood cells, 3.0 million per cubic millimeter; hematocrit, 28%; white blood cells, 5900 per cubic millimeter; neutrophils, 67%; lymphocytes, 31%; monocytes, 2%; reticulocytes, 5.8%; platelets, 9,000. The bone marrow aspirate showed an increased number of megakaryocytes, which were nongranular and did not appear to be producing platelets. Repeated L.E. cell tests were negative. Coombs' test was 1 plus. Platelet survival studies showed the survival of infused normal platelets to be practically nil. The Hinton test was positive. Total protein, 7.0 gm.; albumin, 3.6 gm., and globulin, 3.4 gm. per 100 c.c. Total bilirubin, 0.3. Tourniquet test, positive. Bleeding time, 11.5 minutes. There was no clot retraction after two hours at 37° C. An electrocardiogram showed low T waves in Leads 1, AVL and V5–V8, and was interpreted as showing "borderline abnormality due to T wave changes."

The diagnosis was I.T.P., although S.L.E. was suspected in this case from the start because of the positive Hinton test, the 1 plus positive Coombs' test, and the moderate increase in the serum globulins. Treatment with prednisone, 100 mg. a day, was instituted. The platelets rose to 341,000. The patient was discharged from the hospital on August 1, 1955, with instructions to reduce the dose of prednisone gradually. The platelets were maintained at a high level on prednisone, but when the drug was discontinued they promptly fell. Splenectomy was therefore performed on March 15, 1956. Prednisone was given preoperatively, and a platelet level of 642,000 was obtained prior to surgery. (Splenectomy was performed because the platelet levels were not maintained when prednisone therapy was discontinued. Today, with greater experience in the treatment of I.T.P. with prednisone [Dameshek [45]], we know that it is often possible to maintain the platelets at high levels with small doses of prednisone for indefinite periods. In this case, where good response of the platelets to prednisone had been demonstrated, it is quite probable that the platelets could have been maintained at high levels with small doses of prednisone indefinitely, and splenectomy with subsequent relapse thus avoided.)

The spleen weighed 150 gm. Changes consistent with I.T.P. were present. In addition, the small and medium sized arteries showed extensive lamellar perivascular fibrosis.

A *Treponema pallidum* immobilization test on March 20, 1956, was negative.

The platelets stayed at high levels after splenectomy, ranging from 600,000 to 1,000,000, until July, 1956, when they began to fall. On September 18, 1956, they had dropped to 95,000. At this time prednisone therapy was reinstituted. The platelets have been well maintained since then on a dosage of 7.5 mg. of prednisone a day, and 25 mg. a day for five or six days during the patient's menstrual periods.

At the recall examination on August 5, 1957, the patient was in apparent good health. The blood studies showed: red blood cells, 4.6 million per cubic millimeter; hemoglobin, 13.5 gm. per 100 c.c.; white blood cells, 12,000 per cubic millimeter; platelets, 428,000; reticulocytes, 2%; Coombs' test, negative. The L.E. test was now weakly positive; four typical L.E. cells were found after a two-hour search.

The association of I.T.P., a positive Coombs' test, onion-skin lesions in the spleen, false-positive test for syphilis, hyperglobulinemia and a positive L.E. test the diagnosis of S.L.E. was definite in this case.

Case 8. This 40 year old white female was admitted to the New England Center Hospital on April 4, 1954, with a diagnosis of I.T.P. There was a history of easy bruising and petechiae of four months' duration. The patient had been treated briefly elsewhere with cortisone, with apparent rise in the platelets, but the drug had been discontinued. The history and physical examination yielded no findings suggestive of S.L.E.

Blood examination on April 5, 1954, showed: hemoglobin, 12.4 gm. per 100 c.c.; red blood cells, 3.9 million per cubic millimeter; hematocrit, 41%; white blood cells,

8,200 per cubic millimeter; neutrophils, 70%; lymphocytes, 25%; monocytes, 2%; eosinophils, 3%; platelets, 11,820. L.E. cell test and Coombs' test were negative. The bone marrow aspirate showed an increased number of megakaryocytes, which were nongranular and did not appear to be producing platelets.

Splenectomy was performed on April 14, 1954. The platelet response was prompt and good. At the time of the patient's discharge from the hospital, on April 23, 1954, the platelets numbered 559,000.

The spleen weighed 90 gm. Its pathology was consistent with I.T.P. There were no stigmata of S.L.E.

There was a recurrence of purpura about a year after splenectomy. This became severe in February, 1957, and was manifested by petechiae, ecchymoses, menorrhagia and platelet counts of 30,000 to 40,000. Prednisone therapy was instituted in March, with subsidence of the purpura. Ten milligrams a day have been sufficient since then to maintain the platelets and to relieve the bleeding tendency.

In the summer of 1956 the patient had an attack of arthritis, with pain and swelling of both elbows and pain in her left knee. Cortisone gave striking relief.

In April, 1957, the patient developed a rash on her chin and cheeks after exposure to a sunlamp for five minutes a day for four months. There was reddening of the skin, with vascularization. At this time there was some questionable spindling of the fingers. Repeat L.E. cell test at this time was negative.

I.T.P., and subsequent arthritis and discoid lupus, make this a "definite" case of S.L.E.

Case 10. This 28 year old Puerto Rican female was admitted to the New England Center Hospital for diagnostic study on May 22, 1957. She had enjoyed good health all her life until the age of 24, when she developed a severe toxemia with convulsions during the fourth month of her first pregnancy. She was hospitalized at the Mercy Hospital, Florida, and responded to therapy. About a week after discharge from the hospital she began to develop extensive purpuric lesions associated with low platelet counts. The diagnosis of I.T.P. was made. She was treated with cortisone, with a good response of the platelets. They fell again, however, when the cortisone was discontinued. Slight albuminuria and hypertension persisted until two months later, when she delivered a stillborn. Splenectomy was performed four months later, with an excellent response of the platelets. A second pregnancy shortly after splenectomy, with careful supervision and salt restriction, was not accompanied by toxemia, but nevertheless ended in spontaneous miscarriage at five and one-half months in June, 1955. A few months later, about a year after splenectomy, a rash developed, chiefly on the cheeks and left upper arm, after exposure to the sun. This disappeared in several weeks after a trip to New York in October, 1955, and has not recurred even after exposure to the sun. In 1956, about a year prior to her admission, she began to have migratory arthritis involving her fingers, elbows and knees. The fingers have been most frequently affected, and there has been some visible swelling of these joints. L.E. cell tests were positive. The symptoms were controlled with small doses of prednisone and aspirin.

On admission to the New England Center Hospital the patient was asymptomatic and appeared to be very healthy. The positive physical findings included slight atrophy of the skin over the cheeks, a grade III apical systolic murmur, and a liver that was just palpable.

Blood examination showed: hemoglobin, 11.5 gm. per 100 c.c.; red blood cells, 4.5 million per cubic millimeter; hematocrit, 42%; white blood cells, 7,350 per cubic millimeter; neutrophils, 72%; lymphocytes, 27%; monocytes, 1%. There was moderate hypochromia of the red blood cells. Platelet count was 706,000. The bone marrow aspirate was normal except for the absence of stored iron with iron stains. Erythrocyte sedimentation rate was 17 mm. per hour. Total protein, 7.1 gm.; al-

bumin, 4.1 gm., and globulin, 3.0 gm. per 100 c.c. The Coombs' test was negative. Survey for hemorrhagic factors was normal. The urine was normal. Blood urea nitrogen, 9 mg.%. Fasting blood sugar, 88 mg.%. Uric acid, 5.3 mg.%. L.E. cell tests, done repeatedly by both the clot method of Zimmer and Hargraves, and the heparin glass bead shaker method of Conley, were strongly positive. The electrocardiogram was normal.

The sequence of I.T.P., discoid lupus, migratory arthritis, heart murmur and strongly positive L.E. cell test makes this a "definite" case of S.L.E.

Case 12. At age 18 years this white female was admitted to the New England Center Hospital on December 6, 1947, because of severe menorrhagia and metrorrhagia of six months' duration. There had been easy bruising for seven years, and two or three episodes of moderately severe epistaxis in the last four months.

The past history included attacks of rheumatic fever at ages seven and 10. These, the patient stated, consisted of low grade fever, rapid pulse, heart murmur, and pains in the elbows and knees.

Examination on admission revealed fading areas of ecchymosis on the thighs and legs, and a few scattered petechiae. No heart murmurs were heard. The spleen was not palpable. The remainder of the physical examination was normal.

Blood examination showed: hemoglobin, 12.1 gm. per 100 c.c.; red blood cells, 4.0 million per cubic millimeter; hematocrit, 40%; white blood cells, 7,050 per cubic millimeter; neutrophils, 85%; lymphocytes, 11%; monocytes, 2%; basophils, 1%; eosinophils, 1%; reticulocytes, 5.7%; platelet count, 64,000.

Splenectomy was performed on December 8, 1947. The platelet response was excellent; the count was 1.2 million at the time of the patient's discharge from the hospital on December 16, 1947. The reticulocyte count fell after splenectomy to 0.6%.

The spleen weighed 105 gm. and showed extensive inflammatory reaction about the walls of the small arteries.

The patient was not seen again until August 14, 1957, in response to our recall letter. There had been no purpura in the interim. In December, 1955, during a pregnancy, she had had an attack of pain and swelling of several of the smaller finger joints and of the right big toe. Uric acid was reported to be 2.5 mg.%. X-rays were said to be negative. In the summer of 1956 there was an episode of fever, with temperatures ranging from 100 to 101° F., and lasting for about eight weeks. No cause for this fever was found.

Physical examination on August 14, 1957, was normal. The blood examination showed: hemoglobin, 12.6 gm. per 100 c.c.; red blood cells, 4.1 million per cubic millimeter; white blood cells, 9,150 per cubic millimeter; neutrophils, 45%; lymphocytes, 44%; monocytes, 9%; basophils, 2%; reticulocytes, 0.1%; platelet count, 720,000. The L.E. cell and the Coombs' tests were negative.

I.T.P. with splenic perivascular fibrosis fulfills our criteria for a diagnosis of "definite" S.L.E. The history of rheumatic fever as a child, the recent arthritic episode, and the prolonged incident of unexplained fever all serve to substantiate the diagnosis.

Summario in Interlingua

In un serie de 51 consecutive casos de idiopathic purpura thrombocytopenic, subjicite a splenectomia depost julio 1949, revistas e re-examines del patientes resultava in le discoperta de octo "definite," duo "probabile," e sex "possibile" casos de systemic lupus erythematose. Assi al minus 31,4% habeva manifestationes de systemic lupus erythematose altere que purpura thrombocytopenic, e in 15,7% il esseva opinate que systemic lupus erythematose esseva "definitemente" presente.

Ben que le examines de controlo esseva limitate in 27 casos de idiopathic purpura thrombocytopenic, subjicite a splenectomia ante julio 1949, quatro "definite" e duo "possibile" casos de systemic lupus erythematose esseva trovate in iste serie. Assi

14,8% habeva "definitemente" systemic lupus erythematose, e al minus 22% habeva le un o le altere manifestation de systemic lupus erythematose altere que purpura thrombocytopenic. Un plus complete serie de examines de controlo haberea sin dubita revelate un plus alte incidentia. Sed le cifras es satis alte pro non corrumper le signification del procentages pro le periodo post julio 1949. Illos los confirma plus tosto.

Es presentate duo altere casos de "definite" systemic lupus erythematose occurrente post splenectomia pro idiopathic purpura thrombocytopenic sed diagnosticate e operate ante lor transferimento a nostre servicio.

Nostre serie accumulate de casos de systemic lupus erythematose occurrente post splenectomia pro idiopathic purpura thrombocytopenic consisteva de 14 casos "definite" de systemic lupus erythematose, duo casos de "probabile" systemic lupus erythematose, e octo casos "possibile" de systemic lupus erythematose.

Es discutite le criterios pro le diagnose "definite," "probabile," e "possibile" de systemic lupus erythematose. Es presentate un revista del bases pro le conception que fibrose periarterial del splen, lupus discoide, e positivitate del test pro cellulas L.E. es criterios pro le presentia "definite" de systemic lupus erythematose in splenectomisate casos de idiopathic purpura thrombocytopenic.

Non-responsa e recidiva de thrombocytopenia post splenectomia, amontante in iste casos a 35,7%, pare haber le mesme frequentia como in idiopathic purpura thrombocytopenic in general.

Exacerbation de systemic lupus erythematose occurreva in duo del 14 casos "definite" post splenectomia.

Le disveloppamento de systemic lupus erythematose in casos de idiopathic purpura thrombocytopenic non subjicite a splenectomia sed tractate con prednisona non esseva studiate proque omne tal casos es troppo recente. Il es possibile que le droga submerge le manifestationes de systemic lupus erythematose.

Le preponderantia de femininas es notate, e le possibile signification de iste facto ab le puncto de vista etiologic es mentionate.

Le alte incidentia de systemic lupus erythematose in iste serie signala le necessitate de prender su presentia in consideration in omne caso de idiopathic purpura thrombocytopenic. Observationes de controlo a longe vista es essential, proque le presentia patente de systemic lupus erythematose non deveni necessarimente evidente ante que un serie de annos ha passate depost le declaration de idiopathic purpura thrombocytopenic.

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ABSORPTION OF RADIOACTIVE B_{12} IN PATIENTS WITH PERNICIOUS ANEMIA AFTER LONG-TERM ORAL AND PARENTERAL THERAPY *

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Introduction

The Hematology Research Clinic at the Marion County General Hospital in Indianapolis has been in continuous operation since the days when raw liver was used in the treatment of pernicious anemia. During this time more than 400 patients have been treated with oral and parenteral liver extracts, intrinsic factor preparations, and injectable B_{12} solutions. Some of the patients who have been followed continuously and are still reporting to the clinic have been on oral therapy for 29 years; others, on intrinsic factor preparations, parenteral liver or B_{12} solutions for as long as 26 to 27 years.

During the last four years, Schilling [6] assays have been done on 94 patients on whom a diagnosis of pernicious anemia has been made. This procedure has demonstrated that in patients having pernicious anemia, radioactive vitamin B_{12} administered orally in small amounts is not adsorbed from the gastrointestinal tract unless accompanied by a potent source of intrinsic factor such as human gastric juice or desiccated hog gastric tissue. The degree of absorption of the radioactive vitamin B_{12} is indicated by the amount of radioactivity appearing in the urine during the 24 hours following the ingestion of the radioactive vitamin B_{12} and the administration subcutaneously of a "flushing" dose of 1,000 micrograms of nonradioactive vitamin B_{12}. Graded doses of a standardized intrinsic factor preparation have been given, along with radioactive vitamin B_{12}, to the patients to standardize their response for assays in a study on purification of intrinsic factor. Because of recent reports [1, 2, 3, 4, 5] suggesting that a refractory state may develop in some pernicious anemia patients treated with vitamin B_{12} in combination with intrinsic factor concentrates prepared from hog mucosa, we thought the findings in this group of patients might be of interest, particularly because of their long-term therapy.

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Methods and Materials

Choice of Subjects: The patients chosen for this study were those whose physical and mental status was such that it would be possible to collect urine specimens accurately from them; in addition, they would be able to come to the hospital for a series of Schilling assays. Patients treated with parenteral therapy as well as oral therapy were included in the study so that a comparison could be made of the B_{12} absorption with intrinsic factor in the two groups.

All patients were in remission and had normal blood counts. Those on oral therapy reported to the outpatient clinic at monthly intervals. Neurologic examinations were done every three months, blood counts at each visit. Those on parenteral therapy were seen at one- to four-week intervals. The amount of vitamin B_{12} they received was equivalent to 1 μg. per day. Blood counts were done at three-month intervals. With a few exceptions, the original diagnosis was made and the patients were treated on the research ward. Patients did not have impaired kidney functions which might interfere with the assay.

Urinary Excretion of Vitamin B_{12}: The method described by Schilling [6] was used to determine absorption of vitamin B_{12}, first without intrinsic factor, and then with 165 mg. (¾ U.S.P. unit) of intrinsic factor. The amount of vitamin B_{12} ingested for each test was 2.2 μg. (equivalent to 0.10 μg. of Co^{60}). The radioactive B_{12} was given in a capsule, as was the intrinsic factor. The patients were hospitalized in a special metabolic ward where administration of material and collection of urines were done by graduate nurses trained in metabolic procedures. In addition to the standard intrinsic factor preparations, highly purified intrinsic factor was administered to many of the patients.

After the urine had been collected for 24 hours, the total volume was recorded and a 600-ml. sample was removed. The urine was stirred for five minutes with a mixture of 1 gm. of Hy-Flo Supercel and 3 gm. of Magnesol. This slurry was then transferred to a sintered glass funnel and filtered, using vacuum. This procedure was repeated on each urine filtrate to insure the removal of all of the radioactive vitamin B_{12} present. The bottom of the funnel had been removed and the underside of the sintered plate ground smooth. The funnels were placed on a 1¾" by 2" solid thallium-activated, sodium iodide crystal of a Baird-Atomic scintillation spectrometer instrument, and the recovered radioactivity was determined over the entire Co^{60} spectrum. A sample from each lot of the vitamin B_{12}-Co^{60} solution was used as a standard. The standard was prepared by adding 0.1 microcurie of vitamin B_{12}-Co^{60} to 600 ml. of water and the mixture taken through the above procedure. The counts obtained from this standard were increased by a factor of 1.5 for calculation. This standardization was done to correct for difference in geometric configuration of samples counted in capsule and

funnel. The results were expressed in terms of the percentage of the dose of vitamin B_{12}-Co^{60} recovered in the urine.

The intrinsic factor for the Schilling assay was prepared from hog pylorus. It was standardized in patients with pernicious anemia in relapse and had been approved by the U.S.P. Antianemia Advisory Board. In the assay, each patient received the intrinsic factor preparation with 15 μg. of vitamin B_{12} orally for 36 consecutive days. All of the anemic patients had an adequate reticulocyte response and obtained complete remission. A 165-mg. dose represented 75% of the amount of intrinsic factor which, when combined with 15 μg. of vitamin B_{12}, had been shown to equal one oral U.S.P. unit of activity.

Medications

Oral Preparations

1. Liver Extract 343—Fraction G, 12.75 gm. equivalent to 1 U.S.P. unit.
2. Crude liver-stomach concentrate,* 12 pulvules of which are equal to 240 gm. of fresh liver, and when administered daily will produce a standard response in average uncomplicated cases of pernicious anemia.
3. Semipurified intrinsic factor concentrate with vitamin B_{12}.† Each pulvule contains an amount of intrinsic factor which, when added to 15 μg. of vitamin B_{12}, equals one U.S.P. unit. The content of folic acid is 2 mg.
4. Liver-stomach concentrate with intrinsic factor and vitamin B_{12}.‡ Two pulvules are clinically equivalent to 1½ U.S.P. units. The total vitamin B_{12} content is equivalent to 30 μg. In addition, 600 mg. of anhydrous ferrous sulfate, 150 mg. ascorbic acid and 2 mg. folic acid are present.

Parenteral Preparations

1. A preparation each cubic centimeter of which contains 20 μg. of vitamin B_{12} activity, U.S.P., derived from liver, and 5 mg. thiamin chloride.§
2. Vitamin B_{12} crystalline.‖

Results

Comparison of Schilling Assay Data on Patients Maintained on Intrinsic Factor Preparations with Those Receiving Parenteral B_{12} Therapy: Twenty-four patients have been maintained on oral therapy for from two to 27 years

* Extralin.
† Extralin F.
‡ Trinsicon.
§ Reticulogen.
‖ Betalin 12 crystalline.

(average span, 16 years). The original hematopoietic response in seven was due to Liver Extract 343 (Cohen's fraction G). One patient's first therapy was raw liver. The remaining patients were started on intrinsic factor preparations. Seventeen have received intrinsic factor for more than five years, three for more than 10 years, and 10 for from 21 to 26 years.

In addition to this group, there were 22 patients treated with oral preparations who will be discussed separately.

TABLE 1

Comparison of Schilling Assay Data on Patients Maintained on Intrinsic Factor Preparations with Those Receiving Parenteral B_{12}

		Oral Therapy	Parenteral Therapy
No. patients		24	48
Age (years)	Average	69.8	69.2
	Range	47–83	44–92
Years of therapy	Average	15.9	14
	Range	2–29	2–27
Years on I.F.	Average	13.1	
	Range	0.5–26	
Schilling assay per cent recovery	No I.F.	0.60	0.94
	75% I.F.	8.42*	11.70*
	>75% I.F.	10.83	14.40
R.B.C. (millions)		5.11	4.90
Per cent Hgb.		97.0	89.2

* Significant at 0.01 level.

Forty-eight patients were treated entirely with parenteral therapy for from two to 27 years (average span, 14 years). Their average age of 69.2 years compares closely with that of the oral group (69.8 years). The average number of years on parenteral therapy is practically the same as that on intrinsic factor (13.1 years). The patients in the parenteral group did not receive such therapy because of any suspicion that they might be difficult to maintain on oral therapy. In both groups the type of therapy was based on the interest of the laboratory at the time the patients were admitted, or the ease with which they could be followed in the out-patient department after discharge from the hospital.

The results of the Schilling assays on the two groups are shown in table 1. In addition to the per cent of recovery of radioactive B_{12} in the urine at 0 and 75% intrinsic factor doses, the highest results obtained with

purified intrinsic factor preparations are shown. This is not necessarily the maximal amount of vitamin B_{12} that an individual patient could excrete, but it does show that, with preparations of higher potency than the 75% dose, these patients could excrete a much higher amount of B_{12} than that excreted with a 75% intrinsic factor dose.

There was no statistical difference between the amount of radioactive B_{12} recovered in the urine in the two groups when intrinsic factor was not administered with the B_{12}. When intrinsic factor was administered at the 75% level, the recovery of radioactive B_{12} in the urine of the parenteral group averaged 11.70% ±, compared to 8.42% ± for the oral group. This difference was statistically different at the 0.01 level. In the 47 patients of the parenteral group and 18 patients of the oral group who had received intrinsic factor preparations of higher potency than the 75% standard, the recovery values were practically identical, i.e., 14.4% for the parenteral group, 14.83% for the oral group.

TABLE 2

Urinary Excretion of Vitamin B_{12}-Co^{60} Per Cent of Oral Dose, in Patients Whose Red Blood Cell Count Was Not Maintained on Oral Preparations

Patient	Age	Sex	Original Therapy	Oral Therapy	Parenteral Therapy	Intrinsic Factor	
						None	75%
J. W.	60	W.M.	Crude I.F.—B_{12}	4 yr.	17 yr.	0	16.6
G. W.	67	W.M.	Raw liver then crude I.F.—B_{12}	2 yr.	22 yr.	0	7.3
C. S.	64	W.F.	Human gastric juice L.E. 343 digest then crude I.F.—B_{12}	16 mo.	24 yr.	0.4	8.7
A. P.	71	C.F.	Crude I.F.—B_{12}	19 mo.	19 yr.	0	6.1
H. S.	59	C. F.	I.M. liver ext. then crude I.F.—B_{12}	26 mo.	26 yr.	0	0.4
C. O.	81	W.M.	Liver ext. 343 3 vials daily	19 mo.	27 yr.	0.33	10.1

Since the patients in the oral group as well as those in the parenteral group have had from four to 30 Schilling assays during the last two to three years, with 1 mg. of vitamin B_{12} parenterally with each assay, the red blood cell count and hemoglobin of the intrinsic factor group were compared before and after these assays. Before the assays the red blood count was 4.97 million, hemoglobin, 95.4%; after the assays red blood count was 5.11 million, hemoglobin, 97.0%. The flushing dose of B_{12} did not change what was already a normal blood picture. The patients in the parenteral group had a lower hemoglobin content (89.2%), compared to that of the oral group (97.0%).

Patients Who Were Changed to Parenteral Therapy Because of Decrease in Blood Count While on Oral Therapy: Six patients were placed on parenteral liver therapy, after 16 months to four years on oral intrinsic factor preparations, because of a decrease in red blood cell count. The results of the Schilling assay are shown in table 2. These assays were done between

1955 and 1958. On the basis of the response to a 75% dose of intrinsic factor at this time, the failure of five of these people to maintain a normal blood count cannot be attributed to refractoriness to intrinsic factor derived from hog pylorus. It is not known whether, if refractoriness was present in these patients 17 to 24 years ago, it was lost after the many years of parenteral therapy. In addition, there is no proof that the patients took the oral medication, since the relapse occurred while they were out-patients. When they were admitted to the hospital, parenteral therapy was started without a trial on oral intrinsic factor preparations.

In relation to the possibility that prolonged parenteral therapy with vitamin B_{12} may increase the B_{12} uptake, as judged from the Schilling assay, patient H. S. is interesting. After 26 years on intramuscular liver extract, she showed only a 0.4% recovery of radioactive B_{12}. Her original response was to intramuscular liver extract. On discharge from the hospital, she was placed on three vials of Liver Extract 343 daily. During an acute attack of cystitis and pyelitis her red blood count fell. On Extralin it rose to normal levels. With a recurrence of the urinary tract infection the red blood count fell again and the patient was treated with intramuscular liver extract. As shown in table 6, she responded to higher intrinsic factor doses.

Patient C. O., a white male, differs from the others in this group in that his blood count was not maintained on a nonintrinsic factor preparation, Liver Extract 343. He had not been well since 1898, when he returned from the war in the Philippines where he had contracted malaria. He had had a history of diarrhea since 1915. In 1930 he responded to oral liver extract, but his diarrhea continued. About two months before entering the hospital in 1936 he had stopped taking the liver extract. He had been on intramuscular liver extract thereafter. In March, 1958, he died at the age of 79 (with a normal blood count) from a heart attack while watching television. From his Schilling assay, there was no refractoriness to B_{12} absorption in the presence of intrinsic factor.

In the past it was found [7] that in some patients with pernicious anemia it was difficult or impossible to maintain their blood at normal levels by the administration of the oral therapeutic agents available at that time. The data in this section do not indicate that the patients shown in table 2 were unable to maintain their blood counts in the normal range because of refractoriness to hog intrinsic factor preparations. In most cases, some type of stress such as infection or a surgical procedure caused the need for greater amounts of vitamin B_{12}, or because of the circumstances the patients failed to take the medication.

Patients with Low Urinary Excretion of Radioactive B_{12} with a 75% Dose of Intrinsic Factor: Eight patients who had been classified as having pernicious anemia showed a poor recovery of radioactive B_{12} when hog intrinsic factor in a 75% dosage was administered along with vitamin B_{12}. As shown in table 3, all of these patients were anemic on admission. At

the time of the Schilling assay their blood pictures were normal. With the exception of patient V. L., none had free hydrochloric acid in his gastric juice.

Only one patient, E. B., a Negro female, appeared to be refractory to hog intrinsic factor. This patient with 100 ml. of human gastric juice showed an 8% recovery of radioactive B_{12} in the urine, whereas with a 300% dose of standard hog intrinsic factor no radioactive B_{12} was found in the urine. On admission her red blood cell count was 2.69 million; hemoglobin, 43%; reticulocytes, 0.4%. She was started on an intrinsic factor-B_{12} preparation on her third hospital day, when her red blood cell count was 2.09 million, hemoglobin, 44%, and reticulocytes, 1.5%. A reticulocyte maximum of 8.3% occurred two days later, too soon for a response from

TABLE 3

Patients with Low Radioactive B_{12} Recovery with 75% Dose of Hog Intrinsic Factor

Patient	Sex	Age	Last Therapy Before Schilling Assay	Per Cent Intrinsic Factor							Admission	
				0	75	200	300	400	>400	H.G.J.*	R.B.C.	Hgb.
N. K.	W.F.	68	23 mo. I.F. B_{12}	0.9	0.4		6.1	4.4		3.7	2.58	72
A. J.	W.M.	75	27 mo. I.F. B_{12}	0	0		4.9				1.95	54
L. B.	W.M.	65	21 mo. I.F. B_{12}	0.2	0.3		11.1				2.64	66
N. P.	C.F.	54	26 mo. I.F. B_{12}	0.3	1.3		5.2	8.5			2.04	43
H. S.	C.F.	59	24 yr. I.M. liver extract or B_{12}	1.0	1.3	2.9	3.9	4.2	8.6		3.11	78
O. W.	W.F.	72	46 mo. I.F. B_{12} crude liver-stomach digest	0.3	0.4		0.3			0.2	1.02	28
E. B.	C.F.	62	20 mo. I.F. B_{12}	0	0.4		0			8.0	2.69	43
V. L.†	W.F.	53	18 mo. I.F. B_{12}	2.4	2.4		0.3			0.4	0.65	18

* Human gastric juice—100 ml.
† Gastric pH—1.2.

therapy. The blood count rose to normal levels, ferrous sulfate being added a year later. One year and eight months before a series of six Schilling assays was started, her B_{12} plasma level was 180 $\mu\mu$g./ml.

Two patients, O. W. and V. L., in addition to showing no increase in B_{12} absorption with larger doses of hog intrinsic factor, failed to respond to human gastric juice.

Patient V. L. on admission had a red blood count of 0.65 million and a hemoglobin of 18%. She was so critically ill that a gastric analysis was omitted. Following a transfusion of 1,500 ml. of whole blood and treatment with a hog pylorus-B_{12} combination, a 25.4% reticulocyte rise occurred. The patient was treated for 18 months on the same type of intrinsic factor preparation before she was subjected to a series of Schilling assays. Before the assays her plasma B_{12} level was 180 $\mu\mu$g./ml. After the Schilling assay showed such unresponsiveness, a gastric analysis was done in which a pH as low as 1.2 was found.

Since normal amounts of gastric juice were obtained during the gastric

analysis, 100 ml. of patient V. L.'s gastric juice, along with radioactive B_{12}, were given to a pernicious anemia patient. A 17% recovery of radioactive B_{12} was found in the urine. So here is a patient with malabsorption syndrome who is able to secrete adequate amounts of intrinsic factor but who cannot absorb vitamin B_{12} under the conditions of the Schilling assay.

Patient O. W., another patient with malabsorption syndrome as judged by her failure to absorb B_{12} when 100 ml. of human gastric juice were used in the Schilling assay, differs from patient V. L. in that she could not secrete hydrochloric acid after histamine stimulation. She entered the hospital with a red blood count of 1.02 million, a hemoglobin of 28%, and reticulocytes of 6.8%. On treatment with a dried aqueous extract of hog pylorus plus vitamin B_{12}, a reticulocyte peak of 35.4% was reached on the tenth day of therapy. Reticulocytes subsided to 6.8%, and a second reticulocyte response of 19% occurred on the seventeenth day. Her red blood cell count rose to normal levels, and on discharge from the hospital her medication was changed to parenteral liver extract, and later to injectable crystalline B_{12}.

However, because of reactions to parenteral therapy, this patient was placed on an oral intrinsic factor-B_{12}-crude liver-stomach combination. After almost four years of this oral therapy, plasma B_{12} level was 120 $\mu\mu$g./ml., and blood count was in normal range. The maintenance of a normal blood picture in this patient might be explained by storage of vitamin B_{12} in the liver during the period of parenteral therapy.[8] In contrast, it is difficult to explain the maintenance of normal blood values in patient V. L.

Patient A. J. is an interesting case not only from a clinical point of view but also from a sociologic one. He apparently enjoys alcohol, and on several occasions has been picked up by the police in a stuporous state. In addition, he survived being struck down by an automobile on a busy downtown street. He was first treated for pernicious anemia in 1954, when his red blood count was 1.93 million, hemoglobin, 54%, and reticulocytes, 1.8%. He was started on Extralin F, one capsule daily, with a reticulocyte peak of 22.1% on the sixth day. He was discharged in one month with a red blood cell count of 4.26 million and hemoglobin of 85%. He felt so well that he thought he was cured, so when he had finished the bottle of medicine he had received when he was discharged he did not return to the hospital until one year later, in relapse, with a red blood count of 1.08 million and a hemoglobin of 27%. He was again given an intrinsic factor-B_{12} combination, which caused a reticulocyte rise of 42% on the sixth day. In one and a half months his red count was 3.8 million and hemoglobin was 81%. From that time his blood count has remained normal on Extralin F, although he has not been too faithful about reporting to the clinic. His last admission was in December, 1958, when he was brought in because of a cerebral vascular accident. His red blood count remained normal at 5.57 million. Hemoglobin was 125%. He was discharged to a nursing home.

His low Schilling values cannot be accounted for by poor kidney func-

tion. On his last admission his urea clearance was 62% and 15-minute phenolsulfonphthalein was 12.1%. His plasma B_{12} value decreased from 650 $\mu\mu$g./ml. in June, 1956, and 230 $\mu\mu$g./ml. in July, 1957, to 98 $\mu\mu$g./ml. on last admission. Part of the decreased levels is probably due to his not taking medication regularly. With increasing amounts of intrinsic factor, radioactive B_{12} excretion reached the normal range.

The remaining patients in table 3 also show radioactive B_{12} recoveries in the normal range when larger doses of intrinsic factor are administered. Patient M. K., when tested with human gastric juice, showed no higher results than with hog intrinsic factor. These data agree with those of Berlin et al.,[9] who reported similar findings in patients with pernicious

TABLE 4

Patients Treated for Pernicious Anemia Having High Radioactive B_{12} Recovery in Schilling Assay

Patient	Age	Sex	Therapy Years				Gastric pH				Per Cent Recovery B_{12}	Admission	
			Oral	I.F. B_{12}	I.M. B_{12}	Total	F	20'	40'	60'		R.B.C.	Hgb.
W. L.	72	C.M.	19	11	0.3	19	5.7	1.2	1.2	1.4	7.4	N	N
A. G.	78	W.F.	4	4	23	27	7.7	8.2	7.5	7.7	15.2	3.8	83
M. K.	78	W.F.	9	9	8	17	7.0	7.1	7.0	7.0	17.1	N	N
M. D.	48	W.F.	0.1	0.1		0.1	7.3	7.5	7.7	7.6	14.8	2.15	69
B. W.	75	W.F.	12	4		12	8.2	8.6	8.6	8.6	6.6	N	N
J. W.	60	W.F.			10	10	7.8	8.1	8.2	8.2	12.7	1.74	31
S. S.	53	C.F.			12	12	7.0	7.2	7.6	7.6	5.2	0.87	20
I. C.	52	W.M.	0.1		19	19	8.2	5.8	3.4	6.6	13.5	1.89	49
H. R.	68	W.M.	3.7	0.2		3.7	7.2	7.0	7.0	6.4	3.2	4.08	85

anemia having low urinary radioactive B_{12} recoveries with a standard dose of hog intrinsic factor. When they administered larger doses of purified intrinsic factor, their patients showed a progressively greater excretion of radioactive B_{12}.

Patients Who, on the Basis of Schilling Assay, Cannot Be Classified as Having Pernicious Anemia: An interesting group of patients is presented in table 4. All have been treated with oral or parenteral liver preparations for from one month to 30 years. With the exception of patient J. C., a diagnosis of pernicious anemia had been made. J. C., because of a gastric pH of 3.4, was classified as a nutritional anemia. Yet all of them, when given radioactive B_{12} alone, had values in the Schilling test that fell in the normal range. Only four of these patients (M.D., J. W., S. S. and J. C.) were seen in our clinic in hematologic relapse. The remaining patients were referred to us by other hospitals, physicians, or social service.

Patient J. W. presents an unusual story. She had been used for teaching purposes as a perfect example of a response to vitamin B_{12} therapy. On admission to the hospital in December, 1948, her red blood cell count was 1.74 million, hemoglobin, 31%, and reticulocytes, 1.6%. With a markedly

megaloblastic bone marrow typical of pernicious anemia, and strongly alkaline gastric secretion, she was first treated with experimental parenteral preparations and then with crystalline vitamin B_{12} intramuscularly. The response is shown in figure 1. Here is a woman who has had an anemia since 1935, first being treated with yeast and Haliver oil, who responded typically to parenteral therapy and who, by the standards of the Schilling assay, cannot be classified as having pernicious anemia.

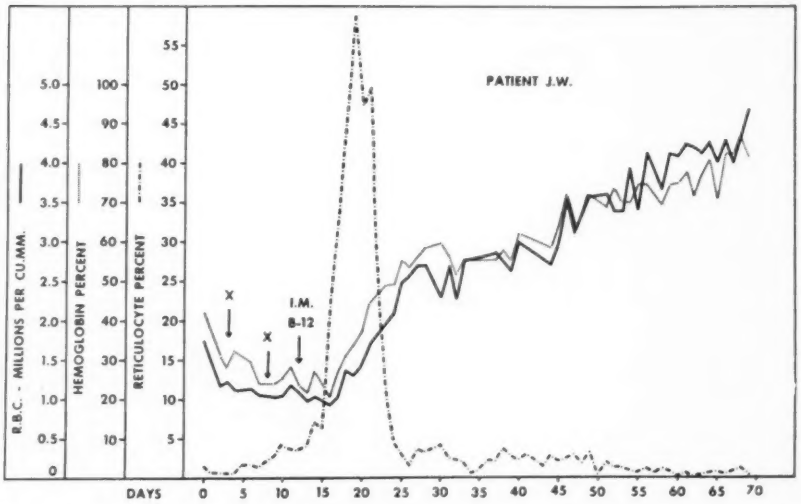

FIG. 1. The response to intramuscular crystalline vitamin B_{12} in patient J. W. who, on the basis of a Schilling assay, cannot be classified as having pernicious anemia.

Patient M. D. also has an interesting history. She was 46 years old when admitted in December, 1956. She was thought to have pernicious anemia because of a red blood cell count of 2.15 million, hemoglobin of 69%, a megaloblastic bone marrow typical of pernicious anemia, and an alkaline gastric juice. The patient admitted taking an occasional drink of alcoholic beverages, which on further investigation was found to amount to one pint of wine a day. Before an antianemic preparation was given, a spontaneous reticulocytosis of 14.9% occurred. On January 22, 1957, when the reticulocytosis had subsided and the red blood cell count was 3.54 million, hemoglobin, 83%, and reticulocytes, 1.1%, an intrinsic factor-B_{12} combination was started. An additional reticulocyte rise of 3.5% occurred. The patient was discharged on February 2, 1957, with a red blood cell count of 3.69 million and a hemoglobin of 79%. On the day of discharge, a Schilling assay was done, with a 12.5% recovery of radioactive B_{12}. A repeat assay on March 25, 1957, showed a 17.1% recovery. Because of these findings, her medication was stopped on April 19, 1957, when her red

blood cell count was 4.76 million and hemoglobin was 90.3%. By March 5, 1958, her red blood cell count had dropped to 2.93 million and hemoglobin to 70%, at which time she had been re-admitted to the hospital.

The report on the bone marrow showed an active bone marrow with granular cell hyperplasia. Red blood count was normoblastic except for one or two suggestive megaloblasts. Numerous macropolycytes were seen. Plasma cells were slightly increased. No abnormal cells were found. Folic acid of the plasma was as low as 0.0006 μg. per 100 ml. The B_{12} in plasma was in the normal range—360 $\mu\mu$g. per milliliter. Liver biopsy showed Laennec's cirrhosis. The patient was treated with folic acid, with improvement in her blood picture. She was discharged on April 3, 1958.

Gastric analysis on patients W. L. and A. G. was not done in our laboratory until after the Schilling assays were completed. These patients were referred to our clinic with reports of no free hydrochloric acid. When the gastric analyses were performed with histamine, the gastric juice of W. L. had a normal acidity, whereas that of A. G. was definitely alkaline. The many years of intrinsic factor ingestion in patient W. L., as well as in others on the same therapy, did not cause refractoriness to hog intrinsic factor.

S. S. was a severely anemic and mentally confused patient when first seen. She had an achylia gastrica and a megaloblastic bone marrow. A good clinical response resulted from parenteral liver extract (equivalent to 1 μg. vitamin B_{12} daily). With a 5.2% recovery in the Schilling assay, this patient had a relative deficiency in intrinsic factor, since exogenous intrinsic factor at the 75% level increased the excretion to 14% of the ingested radioactive B_{12}.

The gastric analysis on patient J. C. was done before therapy was started. This patient had had diarrhea, nausea and vomiting for three to four months before entering the hospital. With a megaloblastic bone marrow, a red blood cell count of 1.46 million, and a hemoglobin of 42%, he was treated with Liver Extract 343, with a reticulocyte maximum of 13.3%. When his red blood count was 3.67 million and his hemoglobin 90%, he was changed to injectable liver extract, without a further reticulocytosis. With the latter therapy, his blood picture has remained in a normal range to the present time.

Another patient, H. R., also had one fraction of gastric juice in the gastric analysis that was slightly below pH 7.0. He has been treated since 1951 (with the exception of two months on an intrinsic factor preparation) with oral B_{12} and folic acid, and has maintained a normal blood count.

The pH values of the gastric secretion of the patients listed in table 4 are of especial interest. With the exception of W. L., all of the patients would have been considered to have no free acid in their gastric juice if Töpfer's reagent, which has an endpoint of 2.8 to 3.4, had been used as an indicator. Even if a pH of 7.0 or above were used as a criterion for the

absence of hydrochloric acid secretion, six out of nine patients would have been classified as having pernicious anemia. Mucus has a pH varying from 7.5 to 8.7, according to various authors,[10] with an average of about 8.2. Since the acidity of the gastric juice depends upon the ratio of mucus to hydrochloric acid secreted,[11] it is plausible to assume that when gastric juice with a pH under 7.8 is obtained in a gastric analysis, some activity of the parietal cells still remains.[10] Apparently a dysfunction of the gastric cells which produce hydrochloric acid can occur without a parallel decrease in the activity of the cells which secrete intrinsic factor.

Goldhamer [12, 13] has shown that intrinsic factor is present in the gastric juice of patients in relapse, and that the deficiency of gastric secretion in pernicious anemia appears to be quantitative rather than qualitative. The amount of gastric secretion is greater in induced remission than in relapse. The patients named in table 4 were in remission. So in spite of the high gastric pH, enough intrinsic factor was present to cause the radioactive B_{12} excretion to be in the normal range.

Keuning et al.[14] have shown by autoradiography of sections of rat stomach incubated with radioactive B_{12} that the chief cells of the fundus presumably elaborate Castle's intrinsic factor. The oxyntic cells (hydrochloric acid cells) do not bind radioactive B_{12}.

Discussion

The findings in this paper agree with those of Schwartz et al.,[15] who state that patients treated with preparations of crude pylorus develop refractoriness to hog intrinsic factor either not at all or to a negligible extent.

Of 35 patients with pernicious anemia treated with various intrinsic factor preparations used in this study, no patient on an oral preparation containing crude liver-stomach digests showed refractoriness to hog intrinsic factor on the basis of the Schilling assay. One patient (O. W.), on the preparation containing the crude digest, had a negligible recovery of B_{12} in the urine on both human gastric juice and hog intrinsic factor.

On the other hand, a patient who had received only an antianemic preparation containing semipurified hog intrinsic factor and vitamin B_{12} appeared to be refractory to hog intrinsic factor in the Schilling test. This patient (E. B., table 6) is a Negro female who had syphilis for many years. With a 300% dose of standard hog intrinsic factor, a negligible amount of radioactive B_{12} was recovered in the urine; whereas, with 100 c.c. of human gastric juice, 8% of the administered dose of B_{12} was recovered. Before the assays she had been treated for 20 months. Five other patients of the 11 on this preparation showed lower-than-normal response to the 75% dose of intrinsic factor, but with larger doses a normal excretion occurred. In all of these patients the blood count was maintained at normal levels.

Berlin et al.[16] have brought up the question as to whether refractoriness could develop independently of oral therapy in patients with pernicious

anemia. Of the 49 patients treated with parenteral therapy in this study, only one (H. S., table 6) did not excrete radioactive vitamin B_{12} in the normal range with a 75% dose of intrinsic factor. Larger doses of intrinsic factor, however, caused radioactive B_{12} excretion in the normal range in this one case. As with the oral group, patients in the parenteral group showed considerable variation in the response to the 75% dose of intrinsic factor in the Schilling assay, the range being from 3.42% to 23.4% recovery of the radioactive B_{12}. Berlin et al.[16] have also noted this variation, and speculated as to whether this might be an expression of different stages of development of pernicious anemia. Since in this study there are seven patients who have been on oral therapy for from 27 to 29 years with a 6.7% to 13.5% recovery of radioactive B_{12} on the 75% intrinsic factor dose, and another five patients on parenteral liver or B_{12} for from 25 to 27 years with a range of 8% to 18%, there appears to be very little likelihood of any progressive loss of the ability to absorb B_{12} in these long-term subjects.

Patient J. C. (table 4) is interesting in that 18 years ago, before the Schilling assay was performed, his gastric juice after histamine stimulation had a low concentration of hydrochloric acid. Since after 18 years the absorption of radioactive B_{12} was normal, there must have been little or no progression in his case.

Another finding of interest in this study is that nine patients have been treated for from four to 30 years with oral or parenteral B_{12} preparations, yet, according to Schilling assays, all absorb B_{12} in the normal range. Five of these patients had been referred to us and were not seen when they had low blood counts. Four had red blood cell counts of 0.87 to 2.15 million on admission to our clinic. In six, pH was above 7.0 in all fractions of gastric juice after histamine stimulation. Only one of the patients had a gastric analysis in the normal range. Nine of the 94 patients presented in this study do not have pernicious anemia on the basis of a normal response in the Schilling assay. Two more appear to have a malabsorption syndrome. The gastric juice of one of these patients, when used as a source of intrinsic factor in a Schilling test in a pernicious anemia patient, caused a high recovery of the ingested radioactive vitamin B_{12} in the urine. The findings in this paper demonstrate the great usefulness of this assay in the study and differential diagnosis of the anemias.

Summary and Conclusions

1. Patients with pernicious anemia treated with antianemic preparations containing crude liver-stomach digests did not develop refractoriness to hog intrinsic factor preparations as judged by the Schilling assay.

2. Of 11 patients treated with a semipurified hog intrinsic factor-B_{12} combination which did not contain liver-stomach digests, one developed refractoriness to hog intrinsic factor. This patient responded to human gastric juice. Five other patients treated with this preparation excreted

small amounts of radioactive B_{12} in the Schilling test, but, with larger amounts of hog intrinsic factor, this blockage was overcome.

3. Of the 94 patients in this study who had been treated for pernicious anemia for from one month to 30 years, nine absorbed vitamin B_{12} normally as judged by the Schilling technic.

4. Two patients were found to have malabsorption syndrome. The gastric juice of one of them had normal amounts of intrinsic factor when tested in a patient with pernicious anemia.

5. The Schilling assay has proved to be a valuable tool in the study and differential diagnosis of the anemias.

ACKNOWLEDGMENTS

The authors wish to thank Dr. C. N. Rice, Mr. J. L. Federman and Mr. W. E. Baum for the processing and assaying of urines for radioactive B_{12} Co^{60}. We also wish to express our appreciation to the members of the nursing staff for their fine coöperation. We are especially indebted to Miss Helen Noble for scheduling patients for the Schilling assays, and to Miss Helen Wagoner for help in preparing the manuscript.

SUMMARIO IN INTERLINGUA

Le methodo describite per Schilling pro le determination del absorption de vitamina B_{12} esseva applicate a 94 patientes pro qui le diagnose de anemia perniciose habeva essite establite. Certes del patientes habeva recipite therapia oral depost usque a 29 annos. Alteres habeva essite tractate con preparatos de factor intrinsec, con administrationes parenteral de extractos hepatic, o con solutiones de vitamina B_{12} depost usque a 26 o 27 annos. Omne le patientes esseva in remission e habeva normal numerationes de sanguine e normal functiones renal.

A causa de recente reportos que suggere que un stato de refractorietate pote disveloppar se in certe patientes con anemia perniciose tractate con vitamina B_{12} in combination con factor intrinsec in concentratos preparate ab mucosa porcin, il esseva opinate que le constatationes in in iste gruppo de patientes esserea de interesse, specialmente in vista del prolongatissime cursos de therapia que illes habeva recipite.

Esseva trovate que patientes con anemia perniciose qui es tractate con oral preparatos antianemic continente crude extractos hepato-gastric non disveloppava refractorietate a preparatos de factor intrinsec porcin, a judicar per le resultatos del methodo de Schilling.

Inter 11 patientes tractate con un combination de semi-purificate factor intrinsec porcin e vitamina B_{12} non continente extracto hepato-gastric, un disveloppava refractorietate contra factor intrinsec porcin. Iste patiente respondeva a succo gastric. Cinque altere patientes tractate con iste preparato excerneva micre quantitates de B_{12} radioactive in le test de Schilling, sed quando le quantitate de factor intrinsec porcin esseva plus grande, iste blocage esseva eliminate.

Inter le 94 patientes in iste studio qui habeva essite tractate pro anemia perniciose durante periodos de inter un mense e 30 annos, novem absorbeva vitamina B_{12} normalmente, a judicar per le technica de Schilling.

Esseva trovate que duo del patientes habeva le syndrome de malabsorption. Le succo gastric de un de illes habeva normal quantitates de factor intrinsec quando illo esseva testate in un patiente con anemia perniciose.

Le methodo de Schilling se ha provate un utile instrumento in le studio e le diagnose differential del anemias.

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RENAL PATTERNS IN MYELOMA *

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"Myeloma kidney" is a term descriptive of the pathologic changes associated with lamellated protein deposits in the renal tubules of patients with multiple myeloma. Clinical manifestations of this process heretofore have been only sketchily delineated. Moreover, two other pathogenetic mechanisms, paramyloidosis and secondary hypogammaglobulinemia, may give rise to significant renal abnormalities in myeloma patients. Review of experience with 30 myeloma patients at this hospital disclosed that renal disease is a common guise under which myeloma may masquerade and elude diagnosis. The purpose of this report is to illustrate and classify the diverse renal syndromes which may be encountered in plasma cell myeloma.

Case Reports

Case 1. A 58 year old engineer entered the hospital with low back pain which had begun after his desk chair tipped over one month earlier. Physical examination revealed tenderness over the lumbar spine and sacrum. Blood pressure was 128/90 mm. of Hg. Mentation and speech were inordinately slow, although his wife maintained that he had always been quick-witted. The reason for his mental obtundity became apparent when the nonprotein nitrogen was reported to be 208 mg.%. The urine contained 4 plus albumin, but no formed elements. Specific gravity was fixed at 1.009. The erythrocyte count was 2,900,000 per milliliter; hemoglobin, 7.9 gm.%; erythrocyte sedimentation rate, 155 mm. in one hour (Westergren). At this point multiple myeloma was suspected and was confirmed by sternal marrow aspiration. The urine was negative for Bence Jones protein. Serum sodium and calcium were normal, but serum phosphorus was 9.0 mg.%. Serum proteins totaled 12.0 gm. per 100 ml., with albumin 1.7, and globulin 10.3 gm. per 100 ml. The anemia was not improved by transfusion therapy, and urethane did little to alter the patient's course. Uremic coma supervened five days before death, on the thirtieth hospital day.

At autopsy the bone marrow was diffusely infiltrated with myeloma cells. Renal changes were typical of myeloma kidney, with extensive proteinaceous cast formation. Infection was rampant, with staphylococcal pneumonia, abscesses in the sternal needle wound and subepicardium, and suppurative pyelonephritis superimposed upon the myeloma kidneys.

This patient's azotemia was clearly attributable to chronic renal tubular obstruction, but the blood pressure remained normal. Observations of Snapper [1] and others have made it axiomatic that renal insufficiency in the

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presence of a normal blood pressure should prompt a search for multiple myeloma. The patient with myeloma kidney is suffering from "stopped-up pipes," [2] and this tubular damage most commonly gives rise to normotensive azotemia. It can, however, produce an impressive variety of manifestations, including simple proteinuria, the nephrotic syndrome,[3] water-losing nephritis,[4] and the adult Fanconi's syndrome.[5]

The following patient represents the first reported instance of renal tubular acidosis attributable to myeloma kidney.

Case 2. A 63 year old rancher entered the hospital with diarrhea which had begun five days earlier, after purgation for rectal impaction. He had first consulted a physician one month earlier because of pain in the hands and hips. His arthritis was felt to be atypical, and marked "secondary" anemia was found, with a hemoglobin of 8.8 gm.%, and an erythrocyte count of 2,900,000 per milliliter.

TABLE 1

Electrolyte Values, Case 2

Date (Nov.).....		3	4	5	7	8	9	10	Normal Range
Serum	CO_2	7.7	13.9	17.1	22		14.4	15.8	25–34 mEq./L.
	Na		148	137	150	138	130	135	136–146 mEq./L.
	Cl		117	111	106	105	103		97–107 mEq./L.
	K		1.8	1.8	1.5	3.2	2.7	2.2	3.8–5.4 mEq./L.
	P		2.8						3–4.5 mg. %
	Ca					3.4	3.2	3.4	4.5–5.75 mEq./L.
Urine	Na					81.5			130–200 mEq./24 hr.
	Cl					84.7			170–250 mEq./24 hr.
	K					81.5			40–65 mEq./24 hr.
	Ca					1.0			5.0–15.0 mEq./24 hr.
	P						0.45		0.8–1.3 gm./24 hr.

Physical examination disclosed only weakness, dehydration and evidence of loss of weight. The urine contained 3 plus albumin and granular casts, and the nonprotein nitrogen was 84 mg.%. Serial electrolyte studies showed acidosis, hyperchloremia and hypokalemia (table 1). The patient rallied following vigorous electrolyte replacement, but within 10 days slipped into coma and died.

Autopsy showed myelomatous invasion of bone, myeloma kidneys (figure 1), and arteriolar amyloidosis in the gastrointestinal tract, heart, prostate and bladder. The small intestine was involved in a pseudomembranous enteritis.

This patient's electrolyte studies on admission were characteristic of renal tubular acidosis, a syndrome in which the principal defect is impairment of tubular reabsorption of bicarbonate.[6] There was decreased acidity of the urine, reflected in a low chloride output. Cation deficits occur in variable combinations in this syndrome, and in our patient sodium was spared, although serum calcium and potassium were low. The hypokalemia resisted repletion, a phenomenon reminiscent of primary aldosteronism. Paramyloidosis was largely an incidental finding, except for its possible role in the production of diarrhea prior to hospitalization, and the terminal pseudomembranous enteritis.

That paramyloid is not always a silent partner in myeloma is illustrated in the following case.

Case 3. A 45 year old fisherman was hospitalized because of hypertension, severe weakness and anemia. He had sought medical care for the first time in his life two months earlier, when he had noted progressive fatigability and intolerance to cold. His physician had found hypertension and initiated treatment with reserpine and Apresoline. During the next eight weeks he developed paroxysmal nocturnal dyspnea, ankle edema and cough. Although he had previously been unusually well, his resistance seemed to be lower than usual, in that he had had two bouts of respiratory infection in the preceding six months.

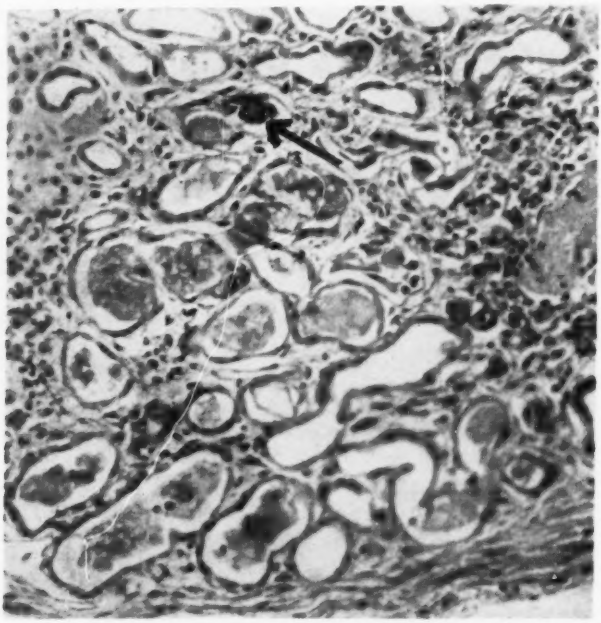

FIG. 1. Myeloma kidney. Renal tubules containing casts of varying stainability, indicating successive deposits. Other tubules show obstructive dilatation. Arrow: giant cell formation adjacent to cast of myeloma protein. (Case 2.)

On physical examination there were pallor, shivering, and a rapid, bounding pulse, with a blood pressure of 210/90 mm. of Hg in both arms. The fundi showed grade 1 hypertensive vascular sclerosis, with flame and streak hemorrhages. The heart was enlarged, and an apical presystolic gallop was audible.

Erythrocytes numbered 2,150,000 per milliliter, and the hemoglobin was 7.4 gm.%. Nonprotein nitrogen was 141 mg.%. The urine contained 4 plus albumin, leukocytes, erythrocytes, and hyaline and granular casts. The erythrocyte sedimentation rate was 92 mm. per hour. Serum albumin and globulin were both at the lower limits of normal (3.7/1.6 gm. per 100 ml.). Roentgenograms of the chest showed cardiomegaly, minimal bilateral pleural effusion, and enlarged hilar shadows consistent with pulmonary congestion. The kidneys were not visualized on attempted intravenous urography.

Initial diagnostic considerations were malignant hypertension with a blood pressure lowered by previous medical treatment, or terminal chronic glomerulonephritis without antecedent history of renal disease.

Congestive heart failure progressed relentlessly despite vigorous therapy, and the patient died after an 18-hour period of relative hypotension (blood pressure, 110/70 mm. of Hg). Autopsy revealed multiple myeloma, with generalized arteriolar paramyloidosis, particularly severe in the kidneys (figure 2).

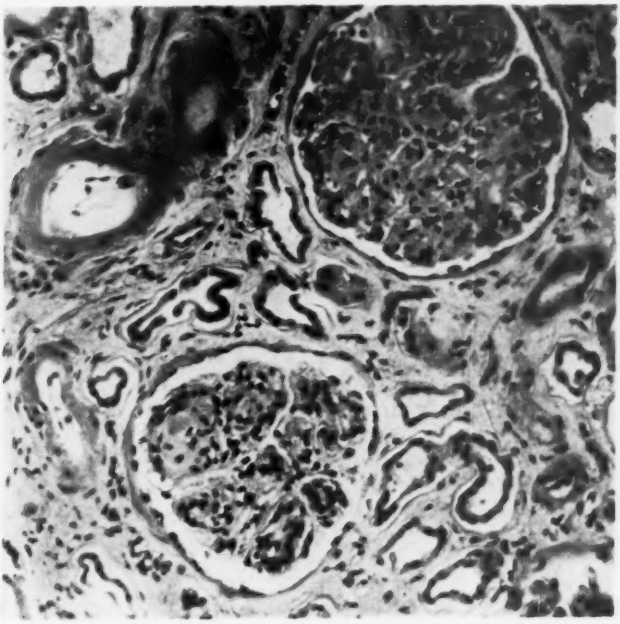

FIG. 2. *Case 3.* Paramyloid deposited in arterioles and in mesangium of the glomerular tufts.

This case serves to emphasize that while normotensive azotemia is quite characteristic of myeloma kidney, in which tubular damage is dominant (case 1), hypertension may occur in myeloma in the presence of paramyloidosis.[1] Hypertension of an "arteriosclerotic" type might reasonably be expected as a result of diffuse arteriolar deposits of paramyloid, a distribution characteristic of the amyloid in myeloma. However, in our patient the hypertension was probably of renoprival (ischemic) origin, as suggested by the hemorrhagic hypertensive retinopathy, since retinopathy does not occur as a result of retinal arteriolosclerosis.[7] The attempt at intravenous pyelography, impelled by the hope of uncovering a correctable renal lesion, appears to have been unwise in the light of reports of sudden death following pyelography in patients with unsuspected myeloma.[8]

Recent studies suggest that the disorder which eventually appears on

the clinical horizon as multiple myeloma may be present for years, in occult, incomplete form, detectable only by search for characteristic protein abnormalities on electrophoresis of serum or urine.[9] In such patients, occult renal involvement may precipitate disaster with disconcerting swiftness after minor stress. This pitfall is illustrated by the following case.

Case 4. A 55 year old retired railroad worker entered the hospital for an apparently innocuous procedure, the removal of a lipoma overlying the sacrum, to which he ascribed burning lumbosacral pain of three months' duration. His physical condition was good, although he had an impressive medical history which included gonorrhea, syphilis, typhoid fever, duodenal ulcer, and a mental illness of uncertain type requiring electroshock therapy. The day after excision of the lipoma he abruptly developed hematemesis, but there was no fall in the blood count from the preoperative values of 5,100,000 erythrocytes per milliliter and 14.0 gm.% hemoglobin. He recovered from this episode with vigorous medical therapy for recurrent duodenal ulcer (confirmed roentgenographically).

During the second and third weeks in hospital the patient complained increasingly of hesitancy and nocturia, although anticholinergic therapy for the duodenal ulcer had been stopped. The prostate was enlarged 3 plus, and on the twenty-second hospital day transurethral prostatic resection was done. Immediately after operation the patient developed fever, spiking to 105° F., anuria, and hyperpnea. The CO_2 combining power was 15.5 mEq./L.; sodium, 130 mEq./L.; potassium, 3.5 mEq./L.; nonprotein nitrogen, 84 mg.%. Urine culture showed a heavy growth of *Escherichia coli* and beta-hemolytic enterococcus. The patient developed fulminant diarrhea, and stool cultures demonstrated *Staphylococcus aureus.* He died four days after prostatectomy.

Autopsy showed bone marrow extensively invaded with myeloma cells, and paramyloid widely distributed in visceral arterioles. In the kidneys there was superimposed hemoglobinuric nephrosis. The patient was not given a blood transfusion, nor was there a period of shock during surgery, and it would appear that hemolysis during transurethral prostatic resection may have been responsible for the hemoglobinuria. Hemoglobin deposits in the renal tubules were not at all severe or extensive, but the disastrous course of events suggests that arteriolar paramyloidosis had rendered the kidneys inordinately susceptible to injury.

Myeloma gave almost no hint of its presence in this patient. Proteinuria was absent in three preoperative urinalyses, and the serum albumin and globulin were normal. In retrospect, it seems clear that the patient's presenting complaint of low back pain, which led to excision of the sacral lipoma, was actually due to myelomatous infiltration of vertebrae.

A somewhat similar course of events in the following case was precipitated by a quite different kind of vulnerability, peculiar to myeloma patients.

Case 5. A 67 year old man was admitted to hospital with an eight months' history of progressive urinary obstruction. During this period he had developed stiffness and pain in multiple joints, with a 12-pound loss of weight.

Physical examination was normal except for a blood pressure of 188/100 mm. of Hg, and limitation of motion in multiple joints. Significant laboratory findings were an erythrocyte sedimentation rate of 64 mm. per hour, a hemoglobin of 8.4 gm.%, and a nonprotein nitrogen of 56 mg.%. There were 17 ounces of residual urine, and some questionable radiolucent lesions in the bony pelvis.

Cystoscopy revealed an enlarged interureteric ridge, which was resected. Postoperatively the patient had fever, chills, hypotension and increasing azotemia, and died on the ninth day.

Autopsy revealed plasmacytosis of bone marrow, diffuse vascular paramyloidosis, and severe suppurative pyelonephritis with abscess formation.

It would appear that insufficient attention was paid to the anemia preoperatively. Although anemia is common in chronic renal parenchymal disease, severe anemia is not a usual result of obstructive uropathy. Simple bone marrow aspiration to assist evaluation of the anemia would have made a startling contribution to the preoperative diagnostic evaluation.

Pyelonephritis, originating on the basis of urinary stasis, became fulminantly progressive in the presence of impaired defenses against infection, and proved to be the proximate cause of death. The unusual vulnerability of myeloma patients to bacterial infections has recently been emphasized by a review of 51 cases of myeloma in which pneumonia occurred 76 times, exclusive of terminal pneumonia, which was the cause of death in one third of the patients.[10]

Discussion

Renal damage is frequent in patients with multiple myeloma, and uremia is second only to pneumonia as a mode of death. In our series of 30 cases, albuminuria and azotemia (nonprotein nitrogen > 40 mg.%) each occurred in 48% of the patients. Renal involvement has occurred in 60 to 90% of myeloma patients in several reported series.[1, 11, 12, 13, 14] The three pathogenetic mechanisms which may involve the kidneys of a patient with multiple myeloma are distinct and disparate.

"Myeloma kidney" refers to a remarkably specific lesion in which protein deposits obstruct and destroy the collecting tubules. In no other renal disease are such large and extensive casts formed. The entire collecting system from proximal tubule to pyramid may be solidly filled with protein. Distinguishing features are lamellation of the casts, indicating layering of successive precipitates, and large multinucleated foreign body giant cells around the casts. Inclusion droplets or crystals are often seen in the tubular cells, and these have been attributed to Bence Jones protein in transport through the cells.

These changes, when fully developed, may enable the pathologist to diagnose myeloma from the kidney sections.[11] However, in some myeloma patients with renal insufficiency the pathologic changes of myeloma kidney cannot be found either in needle biopsies of the kidney[16] or at autopsy.[17] Several alternative mechanisms for the production of renal insufficiency have been suggested, including tubular damage from droplets or crystals of Bence Jones protein, glomerular capillary plugging by inspissated protein or erythrocytes clumped in large rouleaux, and "chronic nephritis," characterized by tubular degeneration and interstitial fibrosis.[16] Armstrong[18] has pro-

vided evidence, recently disputed,[19] that glomerular dysfunction may be more severe than tubular dysfunction in myeloma patients. Clinical patterns resulting from this myelomatous tubular nephropathy have been remarkably varied, and are listed in table 2.

In addition to the tubular syndromes, the clinical picture of acute glomerulonephritis with gross hematuria, chills, fever, headache, edema and hypertension has been reported in patients with myeloma,[20] but no pathologic description of the kidneys in the specific cases cited was furnished.

Paramyloid, found in about 10% of myeloma patients, is characteristically atypical in comparison with true or "secondary" amyloid. Not only does paramyloid fail to take certain stains, which accounts for negative Congo red tests, but it also rarely appears in the parenchymal sites of deposition favored by true (or secondary) amyloid, such as the liver, spleen, kidneys

TABLE 2

Renal Syndromes Associated with Multiple Myeloma

Acute glomerulonephritis
Nephrotic syndrome
Water-losing nephritis
Adult Fanconi's syndrome
Renal tubular acidosis
Acute tubular necrosis
Acute and chronic pyelonephritis

and adrenals. Paramyloid follows the distribution of "primary amyloid" (which with adequate study often proves to be secondary to myeloma[9]), i.e., the mesenchymal tissues of the gastrointestinal tract, subcutis, subendocardium and subendothelial areas of blood vessels. Such arteriolar deposits may occur in many organs, including the kidney, where the resultant ischemia may result in hypertension (case 3), or heightened susceptibility to additional insult (case 4).

Although hyperglobulinemia is common in patients with myeloma, and the increased globulin is often found on electrophoresis to migrate in the gamma zone, many such patients are actually deficient in antibody globulin (secondary hypogammaglobulinemia).[21] This is because globulin synthesis has been perverted in the neoplastic plasma cell, and production of true gamma (antibody) globulin is depressed.[1] This mechanism was probably implicated in the genesis of infections in all five of our patients. In the series cited earlier, 57% of 51 myeloma patients had infections other than pneumonia, predominantly of the urinary tract.[10]

RECENT ADVANCES

Multiple myeloma is associated with an arresting array of metabolic abnormalities (hyperglobulinemia, Bence Jones proteinuria, cryoglobulinemia, pyroglobulinemia, paramyloid), and has attracted a somewhat disproportionate share of the research devoted to neoplasia. Advances in our knowledge of myeloma are consequently accruing at an encouraging tempo.

Electrophoresis has proved to be of greater diagnostic usefulness in multiple myeloma than in any other disease. An abnormal globulin, demonstrable in 75% of patients with multiple myeloma, has two characteristics: (1) an unusually narrow, sharp peak, indicating a great degree of homogeneity, and (2) a strikingly high proportionate concentration, often comprising 70% of the total serum proteins, and in absolute terms reaching values of 10 gm. per 100 ml. of serum. This globulin is synthesized at a remarkably rapid rate, its removal by exchange transfusion being followed by total replacement within five days.[22] More lasting depressions in concentration of the abnormal globulin may occur with urethane or steroid therapy. It has not been possible to correlate the particular type of globulin in a given patient either with the degree of maturity of the plasma cells or with the prognosis.

Ultracentrifugal analysis has shown no distinct difference between myeloma globulin and normal gamma globulin, both proteins having a sedimentation constant of 6.6 Svedberg units. In contrast, a sedimentation constant of approximately 20 Svedberg units is characteristic of the abnormal globulin in macroglobulinemia, a disease which seems to be closely clinically allied to myeloma, with anemia, purpura and plasmacytosis (but no bone lesions).

The similarity in the ultracentrifugal sedimentation constants and in the diffusion constants, which indicate a molecular weight of 160,000 (range: 120,000 to 200,000) for normal gamma globulin and myeloma globulin, suggests that there is no significant difference in shape or hydration between the two types of proteins. Furthermore, isotopic studies have shown that myeloma globulins have half-lives in the range of normal gamma globulin.

However, two important differences between normal gamma globulin and myeloma globulin have been uncovered. Amino end-group analysis has demonstrated that normal gamma globulin contains one aspartyl amino end-group, and either one or two glutamyl groups. Myeloma globulins are abnormal in their end-groups and have been classified [23] into four types on the basis of whether the glutamyl and aspartyl groups were absent (either one or both), or increased. Immunologic technics have shown that myeloma globulins are antigenically different, not only from normal gamma globulin, but also from each other, i.e., each myeloma globulin is patient-specific. Moreover, it does not change its composition during the life of that patient.

All of the above investigational technics have been applied to Bence Jones proteins, and here a more anarchic situation has been found.[24] Bence Jones proteins are extremely individualistic, and differ from each other in electrophoretic mobility, sedimentation and diffusion constants (which indicate variable molecular weights, ranging from 24,000 to 90,000), amino acid composition, and amino end-group analysis (end-groups may be absent or composed of any of a long list of amino acids). Antigenically, Bence Jones proteins show incomplete cross-reactions with each other, with normal gamma globulin, or with the myeloma globulin of the corresponding patient.

Isotope studies have established that Bence Jones protein is not a degradation product of normal body protein or myeloma globulin but is synthesized *de novo* from the amino acid pool. It has an extremely short life within the body, and although the rate of synthesis may reach prodigious heights (excretions of up to 30 gm. per day having been reported), Bence Jones protein cannot be detected in the circulation, even electrophoretically, because of its rapid clearance by the kidney.

Bence Jones protein is highly specific for myeloma. In the sporadic reports of Bence Jones proteinuria in other diseases, either the diagnosis or the accuracy of the test has been open to question. Contrariwise, Bence Jones proteinuria occurs in every patient with multiple myeloma, as shown by immunologic technics.[9] This points up the inadequacy of the usual laboratory tests for Bence Jones protein, which have been found positive in only 10 to 50% of myeloma patients. A rapid and more accurate test for Bence Jones protein, recently described by Scandinavian workers,[25] is now employed in our laboratories.

Therapy remains frustratingly futile in myeloma. Urethane and steroids, alone or together, may produce palliation in some patients, but objective improvement only rarely. Longevity has not been appreciably increased above the average two-year survival time. Recent establishment of a transmissible plasma cell neoplasm in C-34 mice, which results in bone lesions and an abnormal serum protein electrophoretic pattern,[26] provides a basis for hope that experimental development of effective therapy for multiple myeloma may be forthcoming in the reasonably near future.

Summary

Multiple myeloma commonly involves the kidneys and may present clinically in a variety of patterns. Three distinct pathogenetic mechanisms—tubular obstruction by myeloma protein, paramyloidosis, and secondary hypogammaglobulinemia—may be operative in a patient with myeloma.

The renal syndromes produced by myeloma have been categorized, and illustrative cases have been presented, including the first reported instance of renal tubular acidosis due to myeloma kidney.

Recent advances in our basic knowledge about myeloma have been briefly reviewed.

Summario in Interlingua

"Ren myelomatic" es un termino pathologic que describe le alterationes associate con lamellate depositos de proteina in le tubulos renal de patientes con myeloma multiple. Myeloma es capace a producer injurias renal etiam per altere mechanismos, e le revista del experientias de un periodo de dece annos a iste hospital ha revelate que morbo renal es un masca commun de myeloma.

Un ingeniero de 58 annos de etate esseva hospitalisate a causa de dorsalgia e un marcate relentation del parlar e del pensar. Esseva trovate que su nitrogeno nonproteinic esseva grandemente elevate, sed su tension de sanguine esseva normal.

Le constatationes de anemia, hyperglobulinemia, e de anormal cellulas plasmatic in le medulla del sterno confirmava le diagnose de myeloma. Al necropsia, extense quantitates de ancian e nove cylindros de proteina esseva trovate in le tubulos renal. Le infection esseva active in le pulmones, le subepicardio, e le renes (pyelonephritis superimponite).

Un patiente mascule de 63 annos de etate con dolores articular, diarrhea, e debilitate habeva anemia refractori a agentes hematinic. Studios additional revelava albuminuria, cylindros urinari, azotemia, e acidosis. Esseva facite le diagnose de acidosis reno-tubular. Un vigorose therapia de repletion electrolytic resultava transitorimente in un bon responsa, sed le patiente succumbeva con progressive debilitate, edema, e coma. Le necropsia revelava amyloidosis renal associate con myeloma multiple.

Un patiente mascule de 55 annos de etate experientiava exacerbation de symptomas de obstruction urinari durante que ille se trovava sub tractamento pro un sanguinante ulcere duodenal. Post resection transurethral de un grandemente allargate prostata, ille disveloppava diarrhea fulminante, con culturas fecal positive pro *Staphylococcus aureus*. Cessation functional del ren occurreva immediatemente, e le morte del patiente superveniva quatro dies post le operation. Le necropsia revelava "ren myelomatic" con superimposition de moderate grados de nephrosis hemoglobinuric. Myelomatosis afficeva le vertebras e le splen. In retrospecto le diarrhea micrococcal esseva attribuite al relative hypogammaglobulinemia que es characteristic de patientes con myeloma.

Un patiente mascule de 46 annos de etate habeva primo notate debilitate duo menses ante su hospitalisation. Esseva constatate grados sever de hypertension, con albuminuria, azotemia, e hemorrhagia in le fundos ocular. Ille habeva tusse, cardiomegalia, e paroxysmic dyspnea nocturne. Le nivellos seral de albumina e globulina esseva normal. Post un dose medie de reserpina, le patiente suffreva un irreversibile collapso circulatori e moriva post un periodo hypotensive de 18 horas. Le necropsia revelava sever grados de amyloidosis renal, generalisate amyloidosis arteriolar, e myeloma multiple.

In multe casos le correcte diagnose non esseva suspicite durante le vita del patiente e, de facto, non esseva trovate al completion del necropsia grossier. Amyloidosis esseva identificate al tempore del examine histologic, e le subjacente myelomatosis esseva discoperite solmente proque studios del medulla vertebral es un mesura routinari in le necropsias a iste hospital.

Le tres mechanismos per le quales myeloma pote producer morbo renal es: (1) Occlusion del tubulos renal per massive precipitatos de proteina myelomatic, (2) amyloidosis renal, (3) hypogammaglobulinemia secundari, con vulnerabilitate a sever infectiones, incluse pyelonephritis.

Es presentate un revista de recente progressos in nostre cognoscentias fundamental de myeloma.

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DIABETIC ACIDOSIS: AN EVALUATION OF THE CAUSE, COURSE AND THERAPY OF 73 CASES *

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INTRODUCTION

DIABETIC acidosis until recently ranked high among the causes of death in any series of diabetic patients. The fall in mortality in the last few years has been clearly documented by Root.[1] However, the case fatality rate in this complication of diabetes mellitus is still quite significant, and in a relatively recent publication has been noted to vary from 2.4% to 43.7% at a group of large general hospitals.[2]

Among the many factors contributing to the lowering of mortality are the early and adequate use of insulin, the advent of antibiotic therapy for associated and complicating infections, and the better understanding of electrolyte physiology. It has also been found that in this medical emergency the institution of a team effort and an organized approach to the problem has had a significant effect in decreasing mortality.

In an effort to organize the treatment at a large (2,000-bed) municipal hospital where three medical schools maintain separate teaching facilities, an approach to treatment based on current concepts was printed on a standard form made available by the Diabetes Unit to all the Medical and Pediatric Services (Appendices 1 and 2). In each individual case the patient was treated by the service to which he was admitted, usually in consultation with a member of the Diabetes Unit. Therefore, despite the different backgrounds of those actually treating the patients, a certain degree of uniformity was obtained.

Due to difficulties in previous years with overhydration and excess use of sodium in elderly patients with borderline cardiac compensation, and for theoretic reasons as well, the solutions for initial and subsequent replacement of electrolytes and water were hypotonic in composition. They were prepared with modifications * according to the principles of Butler [3, 4] and Nabarro and co-workers.[5, 6] These solutions were standardized throughout

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From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Medical Services, Boston City Hospital, the Department of Medicine, Harvard Medical School, and the Diabetes Service, Boston City Hospital. These studies were aided by USPHS Training Grant #2A-5060.
Requests for reprints should be addressed to Alan S. Cohen, M.D., Department of Medicine, Arthritis Unit, Massachusetts General Hospital, Boston 14, Massachusetts.

BOSTON CITY HOSPITAL

DIABETIC ACIDOSIS SHEET

NAME ..... AGE ..... SERVICE ..... WARD ..... UNIT NO. .....

DATE ..... Use this SHEET for a SINGLE 12-hr. PERIOD ONLY

TIME	CLINICAL STATE						BLOOD							URINE		THERAPY						
Date and Hour	*Mental State	Rect. Temp.	Pulse	Resp. rate	Resp. depth	B. P.	BUN or NPN	B. S.	CO_2	Cl	Na+	K+	Other	Sug.	Ace.	Output Urine	Output Vomit Other	Intake P. O.	Intake I. V. Vol.	Type I. V. Fluid	Insulin	Remarks

GUIDE TO THE MANAGEMENT OF SEVERE DIABETIC ACIDOSIS

I. **Introduction:** Cases include all patients who have a severe degree of acidosis as indicated by symptoms, signs, urinary tests, and a low CO_2. Remember that a diabetic may be in severe acidosis without being in coma, and in coma without being in diabetic acidosis. Attempt to determine and treat the precipitating factor for the acidosis. The patient should be under the care of the Interne supervised by a Resident. Call your visit for any patient who shows no improvement after five hours. The Diabetes Service is always available for consultation and special tests.

II. A. Test the urine for acetone and sugar immediately and thereafter every hour. Constant drainage may be necessary.

B. Draw blood for: culture, sugar, CO_2, Cl, NPN, typing and cross matching. Serum Na and K may be done on consultation with the Diabetes Service.

1. Repeat sugar and CO_2 every 2 – 4 hours. Other chemistries repeated as indicated.

C. Take EKG for base line as soon as possible.

III. **Treatment:**

A. Insulin

1. Immediately upon completion of the above initial urine and blood tests, start treatment with 100–200 u. of reg. insulin s.c. Rarely I. V. insulin (plus s.c. insulin) may be used for the patient in profound shock.
2. Then 50–200 u. (average 100 units) are given every hour until the patient improves. Then cut the insulin dose. In the first twenty-four hours, 500–2000 u. of insulin usually are needed.

B. Fluids

1. Diabetic Acidosis Solution A* (Hydrating Solution)
   a. Once initial insulin is given, infuse I. V. 1500 cc. of Diabetic Acidosis Solution A in 2 – 3 hours depending on the degree of dehydration and the state of shock.
   b. Thereafter proceed more slowly with Solution A. In the average case, only 3000 cc. of this solution is necessary for hydration.
2. Glucose Solution
   a. Change to 5% D/W if blood sugar drops below 250 mg %, or urine tests become green or blue (for question of K therapy at this point see section III, C, 2). If acidosis persists after initial hydration, proceed as above with 5% D/W and Diabetes Acidosis Solution B. Usually not more than 2 – 3 liters are necessary.

CAUTION: Seldom is more than 5 – 6 liters (total) in twenty-four hours necessary. Beware of edema and decreased urine output.

3. Check B.P. every ½ – 1 hour. If shock persists in spite of hydration, transfuse.
4. If possible, start fluids by mouth after four hours, giving especially broths, fruit juices, and milk to combat K and P deficiency.

C. Potassium

After the first four hours of treatment if the urine output is good, all patients should have added potassium in addition to feedings noted above as prophylaxis for possible hypokalemia.

1. If patient can retain fluids P.O. at this time:
   a. Give 2 grams of KCL every four hours for three doses in fruit juice. (1 gm KCL = 13.4 mEq. of K.) This is the safest route to administer K.
2. If the patient cannot retain fluids P.O. at this time, intravenous K may be given. Do not give these solutions in excess of 100 drops per minute.
   a. **Prophylaxis** — Add one vial of Diabetes Solution B† to each 1500 cc of 5% D/W mentioned above in section III B. – 2 until patient is able to take fluids P.O.
   b. **Active therapy** — If there is evidence of hypokalemia by serial EKG's or low serum K, give 2 vials of Diabetic Acidosis Solution B added to 1500 cc. of 5% D/W.

IV. **Additional Procedures:**

A. Start the patient on 300,000 units of penicillin daily routinely. Additional penicillin may be necessary.
B. Obtain serial EKG's every six hours or less for evidence of hypokalemia for the first twenty-four hours.
C. Look for complicating factors especially infection, ruptured viscus, or myocardial infarction.
D. Gastric lavage may help in the patient who continues to vomit or is distended. Use with caution, however.
E. Fill out diabetic acidosis sheet, obtaining all the data required.

Remember that even if the patient is improving from ketosis, watch for possible hypoglycemia, low potassium syndrome and alkalosis as important by-products of treatment.

* This solution contains: Na – 100 mEq., Cl – 60 mEq., and Lactate – 40 mEq. per liter.
† This vial contains: Na – 60 mEq., Cl – 45 mEq., K – 45 mEq., Lactate – 37.5 mEq., P – 22.5 mEq.

APPENDIX 2. Addendum: It is the current recommendation that antibiotics *not* be used for routine prophylaxis, but for treatment of specific infections. Appendix 2 represents the reverse side of the Standard Form used on the Medical Services of the Boston City Hospital when present data were compiled.

the hospital as Diabetic Acidosis Solutions "A" and "B" * (Appendix 2). In addition, large doses of regular insulin early in the course of therapy were

* Diabetic Solution "A" contains: Na^+ Conc. = 100 mEq./L., Cl^- Conc. = 60 mEq./L., $Lactate^-$ Conc. = 40 mEq./L. Diabetic Solution "B" when added to 1,500 ml. of 5% dextrose in water contains: Na^+ Conc. = 60 mEq./L., Cl^- Conc. = 45 mEq./L., K^+ Conc. = 45 mEq./L., $Lactate^-$ Conc. = 37.5 mEq./L., P^- Conc. = 22.5 mEq./L.

recommended, and it was suggested that the patients be transferred to a long-acting insulin preparation as soon as they were well hydrated and out of acidosis. The details of therapy and their results, as well as the characteristics of the patients, will be discussed.

The definitions of diabetic acidosis, ketosis and coma vary in the different series reported in the literature. To avoid the inclusion of mild and easily reversible cases, and to provide a series comparable with several others in the literature, only cases with initial carbon dioxide combining powers of 15 mEq./L. (milliequivalents per liter) or less were included. The patients with carbon dioxide combining powers of 0 to 10.0 mEq./L. are defined in the present paper as being in severe acidosis, while those with carbon dioxide combining powers of 10.1 to 15.0 mEq./L. are defined as being in moderate acidosis.

Included are consecutive cases from October, 1952, when the Diabetes Unit was reorganized and the program standardized throughout the hospital, through May, 1955. In this 32-month period, patients were followed on both Medical and Pediatric Wards and were seen for follow-up in the Diabetes Out-Patient Clinic. The results of therapy and the detailed analyses of the 73 consecutive admissions that occurred during this 32-month (two and two thirds years) period are the subjects of the following report.

Case Material

1. *Admissions and Mortality Rate:* The series consists of 73 consecutive admissions for diabetic acidosis in 52 patients. Eleven of the 52 patients had multiple admissions (table 1); one patient had nine distinct episodes of acidosis, another patient four, a third patient three, and eight patients were admitted twice. There were four deaths in the series. The mortality rate based on the 73 admissions was therefore 5.5%.

2. *Sex:* Twenty-eight (54%) of the 52 patients were female and 24 (46%) were male. Harwood [2] reported almost an equal sex distribution in 57 cases, while Joslin,[7] in his much larger series of 601 patients, remarked

Table 1

Frequency of Repeated Hospital Admissions for Diabetic Acidosis

Number of Admissions per Patient	Number of Patients
1	41
2	8
3	1
4	1
5	—
6	—
7	—
8	—
9	1
Total patients	52
Total admissions	73

on the preponderance of females. Other authors generally report more female than male patients entering the hospital in diabetic acidosis.[8, 9, 10]

3. *Age and Marital Status:* The age distribution is charted in figure 1. The youngest patient was three years old and the oldest, 80. The peak incidence was in the adolescent age group. The average age was 36.6 years. The age incidence reported in the literature is remarkably uniform. Harwood [2] found an average age of 36 years (range, 14 to 75 years); Zieve and Hill,[8] 36.6 years (range, 11 to 77 years); Baker,[9] 31.2 years (range, three to 74 years); Joslin,[7] 29.3 years (range, 11 months to 77.5 years). It is

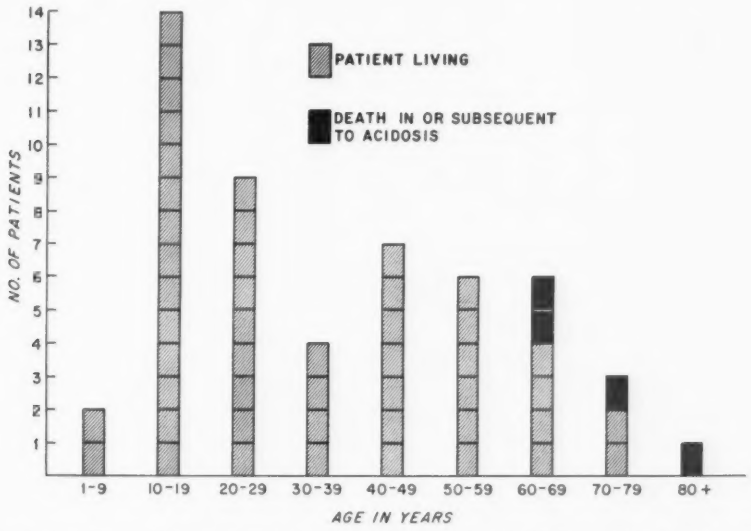

FIG. 1. Age distribution and mortality rate of 52 patients with diabetic acidosis. Note four deaths in patients aged 60 and over.

significant that in the present series the four deaths (see black squares on figure 1) were in patients aged 60 and over; that is, 66, 69, 75 and 80 years old. All of these latter patients had associated severe disease. In this group, 33 patients were single, 20 were married, eight were widowed and one was divorced.

4. *Case Rate per Clinic Patient:* It is difficult to attribute significance to the case rate of diabetic acidosis per clinic patient in a group as heterogeneous in its previous care and follow-up as the present one. However, several authors have suggested this as a method of comparing the various series and assessing the trends in this complication of diabetes mellitus. Only 25 of the patients were known to the Diabetes Out-Patient Clinic. In general, they constituted a group that was resistant to close follow-up (or in some cases, patients were institutionalized and were available only for limited

follow-up) and careful control of their disease. In the years being reported on, the diabetic population followed in the Boston City Hospital Diabetes Out-Patient Clinic numbered well over 2,000. The total number of patients followed per year averaged 1,200. There were about 600 patient visits per month, so that each patient averaged six clinic visits per year. In the 32-month period there would be 19,200 patient visits, so that the diabetic acidosis case rate would be one admission per 640 patient visits to the clinic.*

TABLE 2

Precipitating Factors

		No. of Cases	Per Cent
1. New diabetics		21	29
2. Omission of insulin		20	27
a. Associated with emotional upset	10		
b. Neglect	10		
3. Infection		13	18
a. Acute pharyngitis	2		
b. Severe paronychia	2		
c. Acute pyelonephritis	2		
d. Acute cystitis	1		
e. Bartholinian abscess	1		
f. Bronchopneumonia	1		
g. Acute pelvic inflammatory disease	1		
h. Acute stomatitis	1		
i. Abscess in buttock	1		
j. Acute otitis media	1		
4. Nonspecific gastrointestinal upset		6	8
5. Acute alcoholism		5	7
6. Overeating		3	4
7. Unknown		5	7
Total		73	100

5. *Seasonal Incidence:* It has been proposed that there is an increased incidence of diabetic acidosis in the summer, because of vacations and relaxed living for children and adults alike.[11] Others have suggested that there is a greater incidence of the acute onset of diabetes in the fall and winter, because of the prevalence of respiratory infections in these seasons.[12] In the present report, only two and two thirds years are represented, so that mathematical adjustments have been made for the months of June, July, August and September (figure 2). When the months were then considered individually, peaks were found in July and in February. Seasonal groupings demonstrated that there were almost equal numbers of cases of diabetic acidosis in the winter and spring, with but 12 cases occurring in the autumn, and with the greatest number of cases (27) in the summer. Baker [9] found an increased incidence in the summer, with August as the peak month. Joslin [13] reported more cases in August and October, but little difference in

* The 25 known diabetics followed in the Out-Patient Clinic accounted for 30 of the 73 hospital admissions.

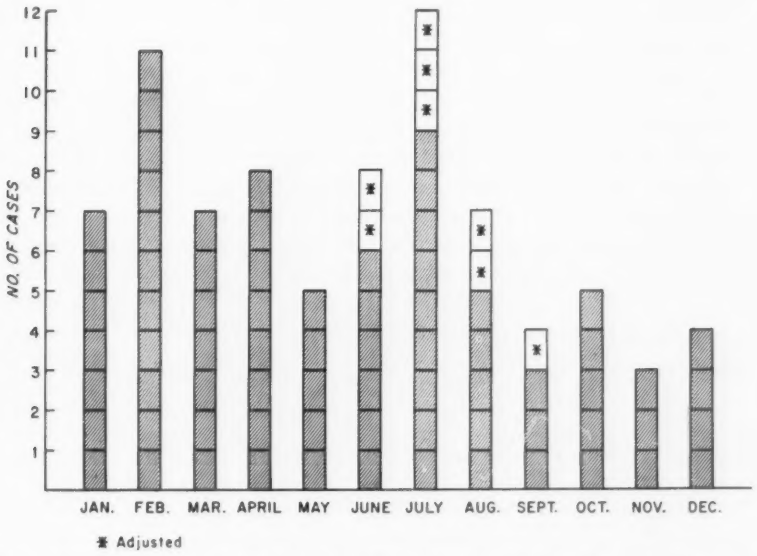

FIG. 2. Seasonal incidence in 73 hospital admissions for diabetic acidosis. Adjusted to three-year period, since total duration of study encompassed two and two-thirds years.

over-all seasonal incidence. Danowski [10] had almost equal numbers of cases in winter, summer and autumn, with a decreased incidence in the spring. Certainly no conclusions can be drawn from these results, but it is clear that diabetic acidosis can occur with frequency in *any* month or season.

6. *Background of the Patients:* Twenty-one of the present 52 patients were admitted and diagnosed as having diabetes for the first time. Among the remaining 31 patients, 16 had had previous episodes of acidosis, and 15 were acidotic for the first time. In the 31 individuals with known diabetes, the average duration of the disease prior to the present episode was relatively long (10.2 years). Joslin [7] reported an average duration of 6.2 years, while Zieve and Hill [8] observed that the diabetes had been present for an average of 5.4 years before the onset of acidosis. In general, it is felt that the greatest incidence of diabetic acidosis occurs during the first year of diabetes.

Not one of the current patients had had previous control that could be classified as excellent or good. Most were quite casual in their approach to the disease and neglectful in keeping clinic appointments, and few carried out in any detail the recommended program for the care of their diabetes. Five of the 31 patients with known diabetes had control classified as fair [14]; none of these had had previous episodes of acidosis. The remaining 26 had poor control.

Most of the patients had severe diabetes and, although not all had a growth onset, all but three were absolutely dependent upon insulin—that is,

they were thin, required large amounts of insulin (30 to 150 units per day; average, 60 units per day), and probably could not have survived without it. Three patients were overweight, and prior to the episode of acidosis two of these had been on no insulin, while the third was maintained on 20 units of a long-acting preparation per day.

A history or previous record of other complications of diabetes was present in a number of patients. Diabetic retinopathy was recorded in 10 patients, diabetic nephropathy (Kimmelstiel-Wilson syndrome) in five, diabetic neuropathy in five, and coronary or peripheral vascular arteriosclerosis in 10. With the exception of the arteriosclerosis, these complications were equally divided among the patients admitted in severe and moderate acidosis.

TABLE 3

Chief Complaint on Admission: 73 Admissions for Diabetic Acidosis

	No. of Cases	Per Cent
1. Nausea and vomiting	26	36
2. Drowsiness or stupor	14	19
3. Entered in coma	11	15
4. Abdominal pain	9	12
5. Excessive thirst	4	5
6. Excessive urination	3	4
7. Blood in urine	1	1.5
8. Difficulty in breathing	1	1.5
9. Sore tongue	1	1.5
10. Congestive heart failure	1	1.5
11. Chest pain	1	1.5
12. Fractured arm	1	1.5
Total	73	100

Arteriosclerosis was roughly twice as common among the patients with severe acidosis.

CLINICAL DATA

1. *Precipitating Factors:* Among the known diabetics, the most common precipitating factor was the omission of insulin (table 2). This occurred in 20 patients (27%), and in one-half of these, specific emotional disturbances were directly related to the omission of insulin. In the other half, negligence in their care was at fault. Literature has slowly been accumulating on the relation of the emotions to diabetes mellitus, not only at the onset of the disease but also during its management.[15, 16] To prevent uncontrolled diabetes and diabetic acidosis, one must not only treat the disease and its complications, but also have a profound understanding of the personality of the patient.

The second most frequent precipitating factor was infection, present in 13 cases (18%). The infections were remarkably diverse in nature and severity, and included two cases of acute pharyngitis, two of acute paronychia, two of acute pyelonephritis, and one each of cystitis, Bartholin abscess, bronchopneumonia, pelvic inflammatory disease, acute stomatitis,

abscess in the buttock and acute otitis media. Six patients had severe gastrointestinal upsets, with nausea, vomiting and occasional diarrhea. If these latter are considered as infectious, then one fourth of the cases were precipitated by infection. Joslin [7] found that 24 of 154 cases (15.6%) of diabetic acidosis were precipitated by infection. In other previously published series, infection, either major or minor, generally ranked high among the precipitating factors of diabetic acidosis, and is listed as the cause of acidosis in from 15 to 50% of the cases.[2, 7, 9, 10, 17] Acute alcoholic bouts were associated with five of the present admissions, and orgies of overeating with three. In five cases no precipitating factors could be found.

As noted earlier, 21 of the patients had previously unknown diabetes. It was difficult to ascertain the exact duration of previous symptoms in this group, although in nine, specific factors that probably accelerated the ap-

TABLE 4

Vital Signs in 73 Patients Admitted in Diabetic Acidosis

	Moderate Acidosis CO_2 Combining Power 10.1–15.0 mEq./L. (31 Admissions)		Severe Acidosis CO_2 Combining Power 0–10.0 mEq./L. (42 Admissions)	
	Mean	Range	Mean	Range
Temperature in degrees (rectal)	99.0	94.6–103	98.5	94.6–105.4
Pulse (beats per minute)	110	80–148	118	65–150
Respiration (breaths per minute)	24	16–64	29	20–50
Blood Pressure	Number of Patients		Number of Patients	
Normal*	26		30	
Hypotensive†	4		8	
Hypertensive‡	1		4	

* Systolic pressure not greater than 140 mm. Hg. Diastolic pressure not greater than 90 mm. Hg.

† Systolic pressure less than 100 mm. Hg. Diastolic pressure less than 50 mm. Hg.

‡ Systolic pressure greater than 140 mm. Hg. Diastolic pressure greater than 90 mm. Hg.

pearance of diabetic acidosis were determined. Seven of the patients had had recent infections (five had pharyngitis, one prostatic abscess, one infectious vulvovaginitis), while one patient had recently had a fractured arm, and one had recently lapsed into acute congestive heart failure.

2. *Chief Complaint on Admission:* Although infections were present in a large number of the patients, the majority at the time of admission complained of symptoms directly referable to their uncontrolled diabetes (table 3). Twenty-six patients (36%) came to the hospital because of severe nausea and vomiting. Although not always a chief complaint in acidosis, nausea and vomiting have been observed in 79% of the patients in a large series of pediatric patients, and in over 65% of the patients in a mixed series.[18, 9]

In the present series, 25 patients (34%) were brought to the hospital because of varying degrees of stupor or coma; 11 (15%) of these patients were completely unresponsive to external stimuli at the time of admission. These figures are similar to those previously reported in the literature.[2, 7, 9, 10, 17] Severe abdominal pain was the chief complaint in nine patients. Seven of these nine were under age 20; the other two were 22 and 48 years old, respectively. This symptom is more common in children, and often is severe enough to mimic intrinsic abdominal disease.[19] Excessive thirst was the chief complaint in four patients, and excessive urination in three. The remainder of the chief complaints on admission are listed in table 3.

3. *Vital Signs:* The vital signs of all patients were recorded at the time of admission (table 4). Although fever was not uncommon in the patients

TABLE 5

Physical Findings at the Time of Admission in Diabetic Acidosis: Correlation with Severity of Diabetic Acidosis as Determined by Carbon Dioxide Combining Power

Physical Finding	Patients with Observation Recorded (Positive or Negative)		Patients with Moderate Acidosis (CO_2 10.1–15.0 mEq./L.) and Observation Positive		Patients with Severe Acidosis (CO_2 < 10.0 mEq./L.) and Observation Positive		Total Patients with Observation Positive	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Dry skin	73	100	28	90	40	95	68	93
Flushed face	54	74	25	81	29	69	54	74
Odor of acetone on breath	68	93	8	26	22	52	30	41
Soft eyeballs	25	34	8	26	17	40	25	34
Kussmaul respiration	67	92	9	29	26	62	35	48
Abdominal tenderness	73	100	12	39	11	26	23	31
Abdominal spasm and rebound tenderness	73	100	3	10	3	7	6	8
Hepatomegaly	73	100	8	26	5	12	13	18
Hyporeflexia	73	100	6	19	15	36	21	29
Hyperreflexia	73	100	0	0	0	0	0	0
Neck rigidity	73	100	0	0	2	5	2	3

with associated infections, a number, particularly those who were severely dehydrated and in a state of shock, were found to be hypothermic. The average rectal temperature in those with either moderate or severe acidosis was normal. It has been stated in the past that fever is not present in uncomplicated diabetic coma, and that indeed, in extremely severe acidosis, the temperature is below normal or normal.[7] One should add that the state of shock and dehydration may mask an underlying fever that becomes apparent when the patient is hydrated and normotensive.

Tachycardia (pulse rate over 100 per minute) was usually present, and was more marked in the patients with severe acidosis. Overbreathing is a very well known accompaniment of diabetic acidosis. As one might have predicted, the patients with severe depression of their carbon dioxide com-

bining powers were found to be more tachypneic (respiratory rate of over 24 breaths per minute). These patients had an average respiratory rate of 29 respirations per minute, while those in moderate acidosis had an average rate of 24. True Kussmaul respiration was observed in 48%—that is, in 62% of those admitted with a carbon dioxide combining power of less than 10.0 mEq./L., and in 29% of those admitted with a carbon dioxide combining power of from 10.1 to 15.0 mEq./L. Danowski [18] has reported overbreathing as one of the most frequent manifestations of diabetic acidosis. In his report of 191 cases, 99% of the patients with carbon dioxide combining powers under 10.1 mEq./L. were tachypneic, and 73% had Kussmaul breathing, while of those with a carbon dioxide combining power of 10.1 to 15.0 mEq./L., only 35% were tachypneic and 4% had Kussmaul breathing.

In the present series, the blood pressure was within normal limits in most patients at the time of admission. Hypotension, however, was observed in 12 individuals (eight of these in severe acidosis), and, indeed, after hydration several of the seemingly normal blood pressures were found to be truly elevated. Five patients were hypertensive at the time of admission. The blood pressure remained elevated in all five after treatment of the diabetic acidosis.

4. *Physical Findings at the Time of Admission:* A review of the physical findings at the time of the admission of the patients to the hospital disclosed that the signs of dehydration were prominent (table 5). Dry skin was observed in 93%, flushing of the face in 74%, and soft eyeballs in 34% of the patients in whom note was specifically taken of the presence or absence of these findings. The odor of acetone was found on the breaths of 41% of the patients, and was observed twice as frequently among the patients with severe acidosis. True Kussmaul respiration was recorded in almost half of the patients, and again was twice as frequent among the patients with severe acidosis.

Examination of the abdomen demonstrated tenderness in 31% of the patients, although abdominal spasm and rebound tenderness were found in only 8%. Positive abdominal findings were slightly (not significantly) more common in patients with moderate rather than severe acidosis. The group of individuals, six in number, with pain, spasm and rebound tenderness on palpation of the abdomen presented the well known but always difficult differential diagnosis of intrinsic intra-abdominal disease. All complained of nausea and vomiting; five suffered diffuse abdominal pain, and one localized lower abdominal pain. All six noted marked diminution of their abdominal symptoms and signs within three to four hours after treatment of the diabetic acidosis had commenced, and complete disappearance within 12 hours. All six recovered fully and gave no further evidence of abdominal disease. It is well known that the abdominal pain and spasm of diabetic acidosis respond to therapy rapidly, and usually a period of con-

servative treatment for three to four hours is indicated before contemplating surgery in these patients.[19]

Enlargement of the liver, a sign often mentioned as being present in uncontrolled diabetes in children, was observed in 13 cases. Five were new diabetics, three of these under age 15, while six were known diabetics, and only one of these was under age 15. All of the patients in the latter group were poorly controlled, and displayed evidence of other complications of long-standing diabetes. The remaining two of the 13 patients with hepatomegaly were alcoholics with known liver disease.

Complete neurologic examinations were carried out on all patients at the time of admission. No patient was hyperreflexic. On the other hand, decreased to absent reflexes were found in 29% of the patients. This observation was made almost twice as frequently in the patients with severe

TABLE 6

Relationship of Severity of Diabetic Acidosis to Blood Sugar Level and Mental Status at the Time of Admission to the Hospital

Blood sugar* (mg. %)	Number of Patients with Moderate Acidosis CO_2 10.1–15.0 mEq./L.					Number of Patients with Severe Acidosis CO_2 0–10.0 mEq./L.				
	Coma	Semicoma	Drowsy	Alert	Total	Coma	Semicoma	Drowsy	Alert	Total
Over 400	2	0	3	4	9	5	4	6	4	19
300–399	0	2	3	8	13	2	5	7	5	19
200–299	0	0	3	4	7	1	0	1	1	3
Under 200	0	0	1[a]	1[b]	2	0	0	0	1[c]	1
Total	2	2	10	17	31	8	9	14	11	42

* Folin-Wu method.
[a] Blood sugar, 191 mg.%.
[b] Blood sugar, 191 mg.%.
[c] Blood sugar, 190 mg.%.

acidosis. Neck rigidity was the only other neurologic abnormality described. It was found in two patients with severe acidosis; both had benign findings on lumbar puncture, and recovered uneventfully after treatment of the acidosis. Since there appears to be such a marked tendency toward diminution of the reflexes in diabetic acidosis, one should be suspicious of concurrent disease (meningitis, trauma, etc.) in patients in diabetic coma who display neurologic abnormalities other than hyporeflexia.

5. *Mental Status on Admission:* The mental status of each patient was evaluated at the time of admission and classified as alert, drowsy, semicomatose (stuporous) or comatose, as determined by the response of the patient to his environment.[20] The individual was said to be in coma when he exhibited a complete absence of response to external (especially painful) stimuli. Semicoma was said to obtain when *only* painful or other disagreeable stimuli elicited a psychologically understandable response. Drowsiness pertained to lesser degrees of clouding of consciousness, while the

patient was said to be alert when he was normally responsive to all external stimuli.

Ten patients were comatose, 11 semicomatose, 24 drowsy and 28 alert at the time of admission to the hospital. The comatose patients generally had greater depression of the carbon dioxide combining power (eight were in the severe acidosis group) and more marked elevation of the blood sugar (seven had levels above 400 mg.%). However, as can be seen in table 6, the converse does not necessarily hold true, for a number of patients with severe depression of the carbon dioxide combining power were not comatose, and many more with blood sugar levels above 400 mg.% were quite alert. In fact, two patients in deep coma were classified as being in moderate diabetic acidosis, since their carbon dioxide combining powers were above

TABLE 7

Laboratory Findings in 73 Patient Admissions for Diabetic Acidosis

Laboratory Determination	Moderate Acidosis (31 Cases) CO_2 10.1–15.0 mEq./L.			Severe Acidosis (42 Cases) CO_2 0–10.0 mEq./L.		
	On Admission		48 Hours After Admission	On Admission		48 Hours After Admission
	Average	Range	Average	Average	Range	Average
White blood count (cells/cu.mm.)	17,600	5,100–29,000	9,200	18,200	5,100–43,000	8,600
Hematocrit (vol.%)	42.4	38–55	40.2	46.5	34–56	41.0
Nonprotein nitrogen (mg.%)	51	28–106	48	54.5	21–177	43.8
CO_2 combining power (mEq./L.)	12.5	10.1–15.0	*	Under 5.0	0–10.0	*
Blood sugar (mg.%) (Folin-Wu method)	358	190–532	†	388	191–599	†

* Not recorded because many patients had received oral feedings or alkali by intravenous route by this time.

† Not recorded because most patients were on oral intake or had received intravenous glucose by this time.

10 mEq./L., and three patients in coma had blood sugar levels between 200 and 399 mg.%. Table 6 also illustrates that the level of the blood sugar was not necessarily related to the mental status of the patient or to the level of the carbon dioxide combining power, although one cannot deny the *tendency* for marked elevations of the blood sugar content, low carbon dioxide combining powers and coma to occur together in greater than random frequency. Kety [21] had concluded that the defect in diabetic acidosis and coma that is primarily responsible for unconsciousness resides in the cellular biochemical processes responsible for the normal utilization of oxygen. He felt that the metabolic acidosis per se might contribute to the depression of cerebral metabolism if these processes are dependent upon environmental pH.

Laboratory Data on Admission

1. *White Blood Count and Hematocrit:* Polymorphonuclear leukocytosis is a common finding in diabetic acidosis. Table 7 shows that comparable increases were found in the white blood counts of the patients with severe acidosis (mean white blood count, 18,200 cells per cubic millimeter) and moderate acidosis (mean white blood count, 17,600 cells per cubic millimeter). The count fell to normal range in almost all cases within 48 hours. The patient with the greatest elevation in the white blood count (43,000 cells per cubic millimeter) had uncomplicated acidosis. Elevations of this magnitude are not uncommon.[7] The routine differential counts carried out on the wards demonstrated a lymphopenia (lymphocytes less than 20 per 100 white blood cells) in 37 of 65 patients, and an eosinopenia (no eosinophils found on routine counts) in 45 of 65 patients. McArthur and coworkers [22, 23, 24] have demonstrated that the eosinopenia and lymphopenia are associated with the increased adrenal cortical activity that is often found in diabetic acidosis. The leukocytosis is attributable to the same factors plus the marked dehydration and infection in a fair percentage of the patients. Further evidence of dehydration is found in the elevation of the hematocrit (particularly in severe acidosis), and its subsequent fall to normal levels within 48 hours (table 7).

2. *Nonprotein Nitrogen:* The mean level of the serum nonprotein nitrogen also fell within 48 hours to normal levels. The elevation and fall were more marked in the individuals with severe acidosis. A number of patients had persistently elevated nonprotein nitrogen levels. This was to be expected, as five patients in this series had known diabetic nephropathy and 10 had generalized arteriosclerosis. Many factors can contribute to the azotemia; these include dehydration and shock, the aforementioned preexisting renal disease, and the excessive protein catabolism of uncontrolled diabetes.[25, 26]

Bernstein [26] noted decreasing renal function in two patients following correction of electrolyte imbalance, and believed that it might represent a manifestation of acute renal failure. Reubi's [27] studies of azotemia in diabetic acidosis indicated that the slowing of the renal blood flow due to increased blood viscosity accounted for the azotemia. In a recent communication Trever and Cluff [28] suggest that, in addition to the initial nitrogen retention seen in many cases of diabetic acidosis, the occasional patient who goes on to increasing degrees of azotemia has had acute renal insufficiency without an evident oliguric phase.

3. *Blood Sugar:* The blood sugar level was determined in all cases by the Folin-Wu method.[29] The majority of the analyses were carried out on an emergency basis, and the sera tested were seldom diluted to 1:20, so that true accuracy could not be obtained in values above 400 or 500 mg.%. For this reason, although levels above 500 mg.% were doubtless present in

some cases, the highest readings were usually reported as "over 400 mg.%," with rare specific readings above this level. Despite this, the average blood sugar in the cases of moderate severity was 358 mg.% (range, 191 to 532 mg.%), and in the severe cases the average was 388 mg.% (range, 200 to 599 mg.%). Averages of 100 mg.% higher have been reported in many series,[1, 8, 10] but most authors indicate that, with the possible exception of exceedingly elevated levels, the blood sugar has little to do with the severity of the acidosis or the prognosis in individual cases. In at least one large series, the average blood sugar was similar to that of the present report.[9]

Despite the above limitations, the present cases corroborate the fact that extreme elevation of the blood sugar is not a necessary accompaniment of diabetic acidosis.[10] One patient had a blood sugar level of 190 mg.%, and two others had levels of 191 mg.%. All three were in undoubted diabetic acidosis, and required large amounts of insulin and fluids for recovery.

4. *Carbon Dioxide Combining Power:* By definition, the carbon dioxide combining power in this series ranged from 0 to 15.0 mEq./L. As stated earlier, a patient was said to be in moderate acidosis when the carbon dioxide combining power ranged from 10.1 to 15.0 mEq./L. (The mean of 31 patient admissions in this range was 12.5 mEq./L.) A patient was said to be in severe acidosis when the carbon dioxide combining power ranged from 0 to 10.0 mEq./L. The mean of 42 patient admissions whose values fell in this range was less than 5 mEq./L. The relationship of the carbon dioxide combining power to the mental status of the patient and to the blood sugar level has already been discussed.

5. *Serum Electrolytes:* Sera were analyzed for sodium, potassium and chloride concentration in the first six hours of admission. The data available before institution of therapy demonstrated the well known fact of initial serum potassium elevation. It ranged from 4 mEq./L. to 7.0 mEq./L. (average, 5.5 mEq./L.). The serum sodium was variable, and ranged from a low of 124 mEq./L. to a high of 150 mEq./L., averaging 136 mEq./L. The average serum chloride content was 99.0 mEq./L. These electrolyte values did not differ significantly in the patients with severe acidosis and those with moderate acidosis. The plasma values, however, are not a true indication of the total electrolyte imbalance, for there is a marked intracellular potassium deficit and a deficit in total sodium and chloride. These will be discussed subsequently.

6. *Urine Sugar and Acetone:* The urinary sugar was reported as 4 plus * in all cases but two. In one of the latter, the urinary acetone was 4 plus; blood carbon dioxide combining power, 10 mEq./L.; blood sugar, 259 mg.%; nonprotein nitrogen, 40 mg.%. In the first four hours of treatment (without added glucose) the urine sugar increased to 4 plus, then diminished with further therapy. In the second patient the urinary sugar was initially 1 plus, as was his initial urinary acetone. The blood sugar level was 305

* By Benedict's test or Clinitest.

mg.%; carbon dioxide combining power, 5 mEq./L.; nonprotein nitrogen, 83 mg.%. With hydration, the patient spilled increasing amounts of sugar and acetone in his urine, and was recorded as 4 plus for both after three hours. With further treatment his course was uneventful. The lack of appearance of sugar and acetone in these cases is probably explained on the basis of altered glomerular filtration rates and tubular reabsorption due to dehydration and diminished renal function. An occasional patient in diabetic acidosis without excessive glucosuria or ketonuria is noted in most series of diabetic acidosis.

Acetonuria was noted in most patients, though it was a maximum of 2 plus in seven patients, 3 plus in four, and 1 plus in four. In recent years the use of the serum acetone has been helpful in determining the presence and, to a degree, the severity of the acidosis.[30] This test was carried out in a number of patients in the last six months of the present study and was found to be a useful adjunct.

7. *Electrocardiogram:* The electrocardiogram gives one a rough estimate of electrolyte abnormalities. It is clear, however, that it may be normal with severe but compensated electrolyte disturbances, or abnormal for reasons other than electrolyte deficits.

In 36 patients, electrocardiograms were obtained at the time of admission or early in the course of treatment. Seventeen of these displayed abnormalities consistent with electrolyte disturbances, 17 were normal, and two gave evidence of other myocardial disease. When the serum electrolytes were restored to normal the electrocardiographic disturbances also reverted to normal. Thus, although there is not universal agreement in the literature regarding the usefulness of the electrocardiogram in depicting potassium depletion,[31, 32] in the present series it was found to be a practical adjunct in following the rehydration and reëstablishment of electrolyte balance.

Therapy

1. *Insulin:* Immediately upon completion of initial urine and blood tests, patients were given 100 to 200 units of regular insulin subcutaneously. Intravenous insulin as well was administered to patients in shock. Patients' subsequent doses were 50 to 200 units of regular insulin subcutaneously at hourly intervals until improvement ensued. The above program was in general usage but was adapted to the needs of the individual patient. The juvenile diabetic in his first bout of acidosis was often controlled with less insulin, while the adult diabetic in deep coma and with complicating infection was given larger initial and follow-up insulin injections.

The average amount of regular insulin given to the patients in moderate acidosis in the first 12 hours was 376 units, in the first 24 hours, 433 units, and in the first 48 hours, 560 units. The patients with severe acidosis as determined by level of carbon dioxide combing power required almost double

these amounts, i.e., an average of 606 units in the first 12 hours, 751 units in the first 24 hours, and 881 units in the first 48 hours.

There appeared to be, in addition, a correlation between the depth of coma (mental status) on admission and the insulin required (table 8). The completely unresponsive patients required even larger amounts of insulin in the early hours of their treatment.

There has been general agreement in the literature [1, 33] that insulin replacement therapy early and in adequate dosage is of the utmost importance. Several recent reports have, however, questioned the value of routine early use of large doses of insulin. Grönberg [34] reviewed 72 admissions for dia-

TABLE 8

Relationship of Insulin Dose to Severity of Acidosis and to Depth of Coma (Mental Status) on Admission

		Average Cumulative Insulin Dose in Units		
Cumulative Hours of Therapy		0–12	0–24	0–48
Moderate Acidosis (CO_2 combining power 10.1–15.0 mEq./L.)				
Mental Status*	No. of Cases			
1	17	193	278	390
2	10	374	440	571
3	2	675	723	915
4	2	1,245	2,435	2,625
Average Insulin Dose for all (31) Cases in Moderate Acidosis Regardless of Mental Status		376	433	560
Severe Acidosis (CO_2 combining power 0–10.1 mEq./L.)				
Mental Status*	No. of Cases			
1	11	393	430	551
2	14	526	547	804
3	9	727	928	1,062
4	8	905	1,161	1,294
Average Insulin Dose for all (42) Cases in Severe Acidosis Regardless of Mental Status		606	751	881

* Mental status: 1 = Alert; 2 = Drowsy; 3 = Semicoma; 4 = Coma.

betic coma, and felt that the clinical course was similar in patients treated with small doses (i.e., less than 100 extra units of insulin over the usual requirement in three days) and those treated with large insulin doses (i.e., over 104 extra units in three days). His series, however, includes a number of cases of mild acidosis, and his conclusions are based to a large extent on the fact that the large dose did not cause acetonuria to disappear any faster than did the smaller dosage schedule. Acetonuria, however, often persists or recurs in carefully treated patients, and in the presently reported series was not related to severity of acidosis, insulin requirement or eventual outcome.

A more careful study of the response of diabetic coma to various insulin

dosages was carried out by Smith and Martin.[35] Forty-three consecutive episodes were treated similarly in all respects but amount of insulin given. Statistical comparisons of three groups (given 80, 160 and 240 units initially and at two-hour intervals) showed no differences in the general responses of the patients. In that study, however, there was a relatively high death rate, i.e., 26% gross mortality and 7% mortality directly attributable to diabetic coma and its complications. A major criticism is that made by Marble,[36] that there is no such thing as the average patient, and that each case must be individually managed.

With reference to the present study, it is apparent that different dosage levels were necessary for patients with varying severity of acidosis and its complications. It appears to be borne out that the lowest mortality rates were found in the series in which individualization of dosage schedule—but generally with prompt use of large amounts of insulin—has obtained.[1, 2] There is an increasing body of evidence that insulin antibodies play an important role in the insulin resistance that develops in diabetic acidosis.[37, 38] The neutralization of this antagonist or antibody with adequate extra insulin to control the acidosis would seem to confirm the fact that large amounts of insulin are often necessary and lifesaving early in the course of the acidosis.

An attempt was also made to start patients on long-acting insulin preparations as soon as the blood sugar was back to near normal and the patients were out of the depths of coma. In this manner, patients could be ambulated earlier, the dangers of prolonged bed-rest in elderly patients avoided, and diabetic regulation more closely approximating that which the patients were usually on could be obtained. In 33 of the 72 admissions, long-acting insulin was utilized before the patient had been in the hospital for 12 hours (usually eight to 12 hours after admission). Nineteen additional patients were given long-acting insulin before 24 hours had elapsed, eight more before 36, and nine in from two to five days.

2. *Water and Electrolytes:* The principles in the use of hypotonic fluids in the therapy of diabetic acidosis have been described by Butler [3, 4] and by Nabarro and colleagues.[5, 6] Simply stated, the diabetic in developing acidosis loses a relatively greater amount of water than of electrolytes. Therefore, hypotonic solutions theoretically would more closely approximate the losses of water and electrolytes that have occurred than would either isotonic or hypertonic solutions. Martin et al.[39] have recently reported a comparative study of hypertonic, isotonic and hypotonic fluids used in the therapy of diabetic acidosis. This study gives further support to the use of hypotonic solutions. They estimated the osmolarity or tonicity of the blood in 26 patients with diabetic acidosis upon entry and again 12 hours later. An increased osmolarity was found in 52% of the group initially, and in 46% 12 hours later. The osmolarity usually decreased or remained unchanged when hypotonic solutions were given, and tended to rise when isotonic or hypertonic fluids were given. With the use of an appropriate

mixture of sodium chloride and sodium lactate (or bicarbonate), the relative concentrations of sodium and chloride in the fluids administered will closely approximate the levels of these ions in the serum. An excess of chloride over sodium is thus avoided.

In the present study, the initial or hydrating solution used intravenously in the majority of patients was the hypotonic solution containing sodium, 100 mEq./L.; chloride, 60 mEq./L.; and lactate, 40 mEq./L. Usually, only 3 L. or less were given, and were followed by normal saline or glucose and, in a few patients, by fructose. Potassium, as a buffered phosphate or solution "B," when given intravenously, was added to the glucose. Whole

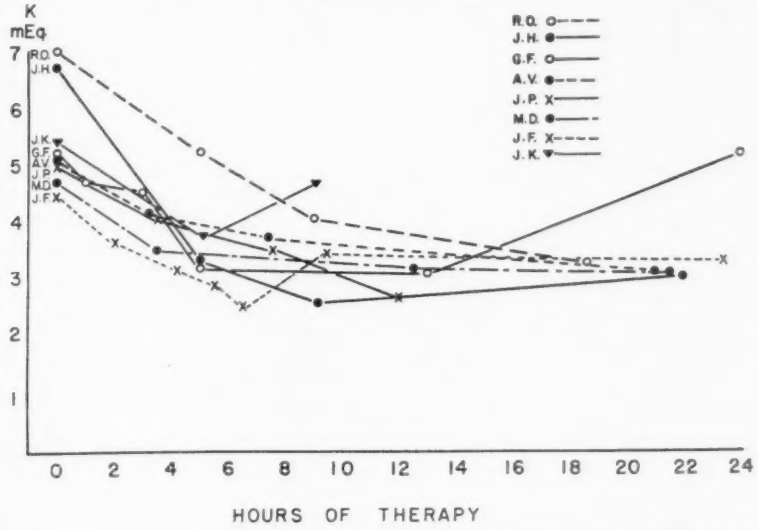

FIG. 3. A representative sample of the behavior of serum potassium levels in eight cases during therapy of diabetic acidosis. The initial serum potassium levels were normal or elevated in this group of patients, and during therapy the level invariably fell. No instances of clinical hypokalemia were encountered.

blood was administered to the patients in persistent shock. The 24-hour average intake was approximately 6 to 7.5 L. of fluids intravenously, containing 325 to 500 mEq. of sodium. Potassium was used intravenously in less than half the patients, and was started after from four to six hours of therapy. Others received potassium by mouth, added to fruit juices. No instances of clinical hypokalemia were encountered, but the serum potassium fell in most patients with therapy (figure 3). The serum sodium levels tended to fall if initially elevated, or to rise if they were low.

The course of a typical patient in severe diabetic acidosis is depicted in figures 4 and 5. In this patient, the serum sodium remained relatively constant except during the administration of 10% fructose, when a fall occurred (figure 4). The serum potassium fell from 4.6 mEq./L. to 2.6

mEq./L. in the first seven and one-half hours, but clinically the patient showed steady improvement. Forty-five milliequivalents of potassium intravenously were sufficient to increase the serum potassium to 3.5 mEq./L. and to maintain it at approximately this level. Potassium administration could have been started earlier in this patient, and would have been if the potassium value had been known. The carbon dioxide combining power rose steadily, and had reached 19 mEq./L. by the tenth hour of therapy. There was a total fluid intake of 7,300 c.c., and a 2,900 c.c. output during the first

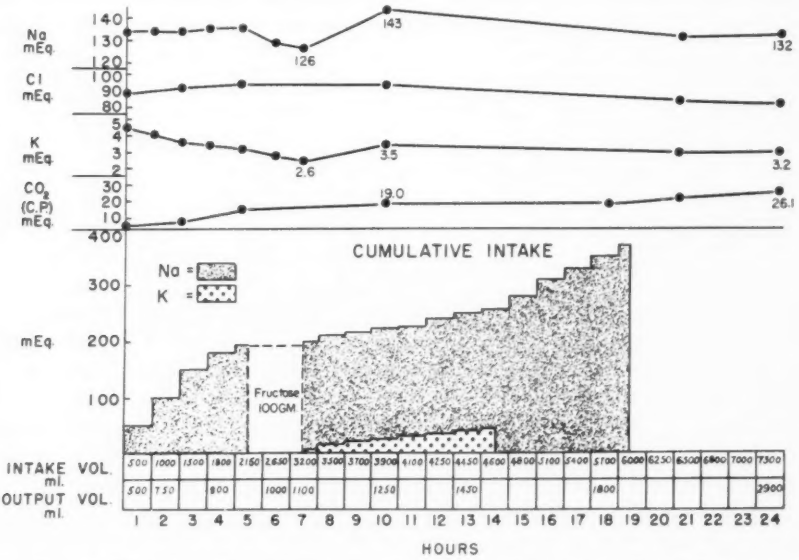

FIG. 4. Electrolyte observations in a patient in severe acidosis treated with hypotonic solutions, case J. F., age 53. The serum sodium remained relatively constant except during the period of the administration of 10% fructose, at which time it decreased. The potassium fell from 4.6 mEq. to 2.6 mEq. in the first seven and one-half hours, but with the administration of potassium intravenously the serum level increased to 3.5 mEq. The CO_2 combining power rose steadily and reached 19.0 mEq. by the tenth hour of therapy. The fluid intake was 7,300 ml., with an output of 2,900 ml. during the first 24 hours of therapy.

24 hours. The admission blood sugar of 540 mg.% had fallen to less than one-half of the original level by the fifth hour of therapy, when intravenous fructose was begun (figure 5). The pyruvic acid level rose with fructose administration. Approximately two thirds of the total insulin administered was given in the first three and one-half hours of therapy. The phosphorus dropped markedly from an admission value of 7 mg.% to 1.1 mg.% in seven and one-half hours. Calcium remained relatively constant.

Thus the hypotonic solutions for initial hydration proved to be satisfactory, and no complications resulting from their use were encountered. The average amount of water and sodium administered was within the

limits suggested by Talbot.[40] As Harwood [2] found, the edema that may occur when large amounts of isotonic saline are given was not encountered. The marked elevations in serum sodium and hyperchloremia occasionally seen when hypertonic and isotonic solutions are given [39] were not observed.

3. *Prophylactic Antibiotics and Catheterization:* When the present series of patients was being treated, it appeared to be prudent to institute prophylactic antibiotics after appropriate cultures of blood, urine, throat, etc., were obtained. In many cases the antibiotics were indeed therapeutic rather than prophylactic, since infection as a precipitating and possibly complicating

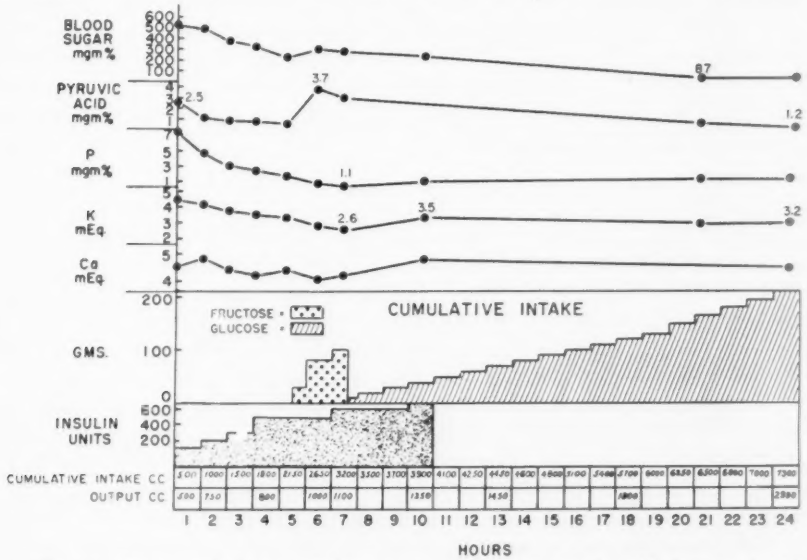

FIG. 5. Some metabolic observations in the therapy of diabetic acidosis treated with hypotonic solutions, case J. F., age 53. The admission blood sugar of 540 mg.% fell to less than one-half the original level by the fifth hour of therapy. The pyruvic acid level, which was elevated on admission but had decreased, rose further when fructose was given intravenously. The markedly elevated serum phosphate level decreased to 1.1 mg.%, but calcium remained relatively unchanged. Approximately two thirds of the total insulin administered was given in the first three and one-half hours of therapy, with the full 650 units being given by the tenth hour.

factor in the debilitated patient seemed to play so great a role. In addition, comatose patients were catheterized, and indwelling catheters were occasionally used. Recent studies by Kass,[41] however, have pointed out the uselessness and, indeed, the dangers of chemoprophylaxis in patients with indwelling catheters. Beeson [42] has further emphasized the necessity of avoiding catheterization whenever possible. In addition, the studies of Weinstein [43] have pointed out the dangers of general antibiotic prophylaxis. Petersdorf and colleagues [44] investigated antibiotic prophylaxis in a group of 72 unconscious patients, including 10 with diabetes mellitus. Their

results indicated that there was no benefit from the prophylactic administration of antibiotic drugs in the patients, and that the procedure was deleterious in several cases.

The current recommendations for patients with diabetic acidosis are for appropriate cultures and smears to be made and antibiotics to be instituted for specific infections. Catheters are to be used only when absolutely necessary, and indwelling catheters to be avoided.

4. *Miscellaneous:* All patients in diabetic acidosis were regarded as medical emergencies, and a physician was in attendance continuously until the patient was deemed to be out of danger. Occasional surgical consultations were obtained in patients with severe abdominal pain. Gastric lavage was performed in patients with severe nausea or vomiting, and in those with evidence of gastric dilatation by physical or x-ray examination. Shock blocks under the foot of the bed and vasopressor agents were used to sustain patients who were markedly hypotensive.

Results and Complications of Treatment

There were four deaths in this series of 73 consecutive hospital admissions. All four were over age 65. The case reports are detailed below. Aside from the four deaths, there were two common complications of therapy. The first, hypoglycemia, occurred in five patients, usually between the twenty-fourth and forty-eighth hours of therapy. In all cases the insulin reactions were transient and easily controlled by oral feedings.

A more common and more serious complication was urinary tract infection. While several patients may have had infections of the genitourinary tract prior to admission, there were nine instances of new or recrudescent urinary infection associated with the use of indwelling catheters for over 12 hours. The dangers of the catheter are highlighted in this series. It became clear that prophylactic antibiotics, particularly penicillin, are useless in preventing these infections, which are usually due to gram-negative organisms.

No instances of severe gastric dilatation were observed. Two patients developed infections about leg vein cutdowns that had been in use because of the state of shock that was present. Both infections were easily controlled. There were no cases of congestive failure precipitated by the use of hypotonic solutions, a complication that had been seen several times when isotonic saline had been in use in previous years.

It was observed that, following the episode of acidosis in the known diabetics who had been maintained on insulin, the discharge insulin requirement was considerably elevated over the insulin requirement on admission. The average amount of insulin being taken at the time of hospital admission was 59 units, whereas at the time of discharge it was 73 units. The reason for this is not known, but it could be associated with a number of factors: (a) the patients had been on insufficient insulin previously, and only now

were on the correct dose; (b) the attack of acidosis had exhausted and indeed eliminated the insulin-producing capacity of whatever few islet cells in the pancreas were previously functioning; or (c) the increase was only transient (possibly still due to insulin antibodies), and would subsequently return to its earlier level.

The length of hospitalization in the group averaged nine days. It was felt that the early use of long-acting insulin and early ambulation accounted for this relatively short hospital stay, and it was not unexpected that the patients who entered in moderate acidosis remained in the hospital for briefer periods of time (average, seven and one-half days) than did those who had entered in severe acidosis (average, 13 days).

Case Reports of Four Deaths

Many factors have been implicated as being of significance in the cause of death in diabetic acidosis. These include length of coma prior to treatment, severity of acidosis, age of patient, previous complications, etc. In this series, deaths occurred only among patients in the oldest age group (i.e., 65 and over). All had evidence of other severe disease. Following are the case reports of the four deaths (with postmortem examination in two).

Case 1. A 66 year old widow was referred to the hospital from a nursing home with a diagnosis of diabetic acidosis. The patient, a known diabetic for the last 10 years, had been in fair control on 30 units of long-acting and 5 units of regular insulin daily. For no apparent reason, the glucosuria had increased to give a red Benedict's test the two days prior to hospital admission. Associated mental confusion, nausea and vomiting were observed on the day of hospital admission.

The past history included an amputation of her left leg for "diabetic gangrene," and the diagnosis of generalized arteriosclerosis.

Examination at the time of hospital admission showed the patient to be an elderly, drowsy, disoriented white female complaining of severe thirst. Odor of acetone on her breath and Kussmaul respirations were not present. Funduscopy demonstrated arteriosclerotic changes in the arterioles. Examination of the chest and abdomen was negative. Cardiac examination demonstrated a grade II apical systolic murmur; the heart was not enlarged to percussion. The scar of a left midthigh amputation was well healed. In the right extremity, the dorsalis pedis and posterior tibial arterial pulsations were absent. Neurologic examination revealed absent knee and ankle reflexes in the right extremity.

The initial urine specimen gave a 4 plus Benedict's test for sugar and 4 plus acetone test; occasional white blood cells and granular casts were observed in the sediment. The white blood count was 9,400 cells per cubic millimeter. The differential count showed that 15% of the cells were young polymorphonuclear cells. The initial blood sugar was 305 mg.%; carbon dioxide combining power, 14 mEq./L.; serum sodium, 156 mEq./L.; serum potassium, 5.0 mEq./L.; serum chloride, 92 mEq./L. The serum nonprotein nitrogen was 42 mg.%. Initial nasal culture showed a few beta hemolytic streptococci and *Staphylococcus aureus.* Throat culture grew out staphylococci with alpha hemolysis. Urine cultures grew a few *Staphylococcus albus* and enterococci. Blood culture on admission was negative. Culture of the left ear demonstrated *Bacillus subtilis, S. albus* and *Bacillus welchii.* Chest

x-ray demonstrated clear lung fields, enlargement of the left ventricle, and an elongated calcified aortic arch. Electrocardiogram revealed a sino-auricular tachycardia, with a rate of 136 and Q-T interval at the upper limits of normal.

During the first 12 hours of therapy the patient received 820 units of regular insulin, 1,500 c.c. of Solution "A," 1,500 c.c. of normal saline and 1,500 c.c. of a mixture of Solution "A" with 5% dextrose in water. The blood sugar fell to 240 mg.%, the carbon dioxide combining power rose to 27 mEq./L., and the nonprotein nitrogen fell slightly, to 36 mg.%. The urinary acetone cleared completely. Due to the disoriented and uncoöperative status of the patient, urine was collected through an indwelling Foley catheter. Improvement continued and the patient was maintained on oral fluids. On the morning of the third hospital day the patient's temperature, which had been normal, rose to 103.6° F. rectally; she became semicomatose, and her blood pressure dropped to 50/0 mm. of Hg. Blood was drawn for blood sugar and cultures, and she then was given 20 c.c. of 50% glucose, without clinical improvement. The blood sugar report was 170 mg.%. It was observed at about that time that the indwelling catheter was partially obstructed. Urine smear and gram stain showed many clumps of white blood cells and gram-negative rods.

The patient was given intravenous fluids, two units of whole blood and intravenous chlortetracycline. On this therapy her blood pressure rose but she remained semicomatose. In spite of all supportive therapy she continued on a downhill course, and died on the morning of the fourth hospital day. The blood culture of the previous day subsequently grew out *Aerobacter aerogenes.*

Clinical Diagnoses:

1. Septicemia, *Aerobacter aerogenes* secondary to acute urinary tract infection.
2. Diabetes mellitus with diabetic acidosis (corrected).
3. Generalized arteriosclerosis, with marked peripheral vascular involvement.
4. Terminal acute pulmonary edema.

Post Mortem:

1. Arteriosclerotic heart disease with congestive heart failure as evidenced by
   (a) Pulmonary congestion and edema;
   (b) Bilateral hydrothorax;
   (c) Hydroperitoneum.
2. Diabetes mellitus with
   (a) Glycogen deposition in liver;
   (b) Glycogen nephrosis;
   (c) Intercapillary glomerulosclerosis.
3. Chronic cystitis.
4. Generalized arteriosclerosis with marked sclerosis of coronary arteries.
5. Fecal impaction.
6. Cultures at autopsy:
   (a) Spleen: cultures grew out *Aerobacter aerogenes.*
   (b) Lung, right lower and left lower lobe: cultures grew out *Aerobacter aerogenes* and *Monilia albicans.*
   (c) Heart blood: cultures grew out *Aerobacter aerogenes.*

Comment: Thus an elderly female diabetic with many of the complications of the disease had an episode of diabetic acidosis the precipitating factors of which were unknown. After successful treatment of the acidosis the patient apparently developed an acute cystitis and septicemia (*Aerobacter*

aerogenes) associated with prolonged use and poor drainage of her indwelling catheter. Aggressive treatment of the infection and shock was unsuccessful, and appeared to be associated with terminal fluid retention and congestive heart failure.

Case 2. A 75 year old widowed housewife was referred to the hospital because of "myocardial failure." The patient had apparently been in moderately good health until four months previous to admission, when weakness, weight loss, polydipsia and polyuria were observed. Although glycosuria was found in a laboratory test, no specific therapy had been instituted by her local physician. The patient later developed ulcers over the feet, which were being treated. Four days prior to admission she became anorectic, complained of weakness, and took to bed. On the night prior to hospital admission she developed marked shortness of breath, and complained of severe thirst and vague aches and pains. She was seen by a physician, who noted that her pulse was slow, weak and irregular, and referred her to the hospital.

On examination at the time of hospital admission the patient was found to be an elderly, semicomatose white female in acute distress. Her temperature was 96° F., her pulse rate, 12 to 16 beats per minute, and her blood pressure, 110/80 mm. of Hg. She was tachypneic, but no odor of acetone was noted on her breath. She was markedly dehydrated and slightly cyanotic. Her neck veins were not distended; her lungs were clear, but her heart was enlarged to percussion. The sounds were distant, but a harsh grade II apical systolic murmur was heard, as well as a split first sound at the mitral area. Rhythm was regular, with a rate of about 12 to 16 beats per minute. Auricular beats were heard in the right third interspace. The abdomen was slightly distended, soft and nontender, and the liver edge was felt six fingerbreadths below the right costal margin. Neurologic examination was unremarkable but for the semicomatose state of the patient.

An electrocardiogram taken at the time of admission showed a wavy line, interpreted as atrial fibrillation with rare idioventricular contractions consistent with "a dying heart." Blood was drawn for chemical studies and the patient was treated for shock, but she slowly became unresponsive, with inaudible heart sounds, over the next half-hour. Insertion of a dry needle into the myocardium caused an immediate response, with a regular heart rate of 72 beats per minute. An electrocardiogram showed idioventricular rhythm with complete A-V dissociation. For two hours this rhythm alternated with a secondary heart block with 3:1 conduction and a ventricular rate of 20. The slower rhythm gradually predominated until the circulation became increasingly inadequate and the patient had grand mal seizures. At this point stimulation with a cardiac "pacemaker" * was begun and maintained over the next 24 hours.

During the first 12 hours urinary output was about 5 c.c. per hour. The urine showed 1 plus to 2 plus sugar and no acetone. The initial blood findings, returned five hours after admission, were reported as: blood sugar, 500 mg.%; carbon dioxide combining power, 9 mEq./L.; nonprotein nitrogen, 128 mg.%; chloride, 84 mEq./L. Electrolytes then drawn were later reported as: serum sodium, 128 mEq./L.; serum potassium, 7.3 mEq./L. During the subsequent 12 hours the patient received 675 units of regular insulin and 4,500 c.c. of Diabetic Solution "A." At the end of that period the blood sugar was 170 mg.%; carbon dioxide combining power, 17 mEq./L.; nonprotein nitrogen 155 mg.%. The initial white blood count, that had been 31,400 cells per cubic millimeter, fell to 17,000, and the initial hematocrit of 36 fell to 32 vol.%. The patient was heavily sedated during this period of electrical cardiac stimulation.

About 36 hours after admission (and 24 hours of continuous existence on the cardiac pacemaker), the patient established and maintained a normal sinus rhythm at

* Courtesy of Dr. Paul Zoll.

a rate of 70, with a tracing showing right bundle branch block. Her diabetes was controlled on small amounts of long-acting insulin and intravenous fluids. Heavy sedation was discontinued and the patient regained consciousness and was alert and voluble.

Urine output now approached 60 c.c. per hour, but the patient was still critically ill and had occasional diarrhea and guaiac-positive vomitus, plus occasional dyspnea. On the third hospital day she had a good diuresis (urine specific gravity, 1.010). On the fourth hospital day she suddenly developed an irregular rhythm, and before an electrocardiogram could be taken was found to be without pulse or respirations. She did not respond to the cardiac pacemaker. Blood chemical studies done 12 hours before death had revealed a blood sugar of 232 mg.%, a carbon dioxide combining power of 21 mEq./L., and nonprotein nitrogen of 77 mg.%.

Clinical Diagnoses:

1. Diabetes mellitus with acidosis.
2. Chronic renal disease with acute renal insufficiency, uremia and ? hypokalemia in the diuretic phase.
3. Multiple cardiac arrhythmias, including second and third degree heart block, intermittent auricular and ventricular asystole ? secondary to potassium intoxication.
4. Congestive heart failure with hepatomegaly.

Post Mortem:

1. Arteriosclerotic heart disease.
   (a) Calcific coronary arteriosclerosis.
   (b) Calcific mitral and aortic valvular sclerosis.
   (c) Myocardial fibrosis of posterolateral wall of left ventricle.
2. Small infarct in papillary muscle.
3. Acute interstitial pneumonitis.
4. Recent splenic infarct and splenomegaly.
5. Central hemorrhagic necrosis of liver.
6. Benign nephrosclerosis.
7. Bilateral hydrothorax.
8. Gangrene of left foot.
9. Generalized arteriosclerosis.

Comment: This 75 year old woman apparently developed diabetic acidosis over a four-month period. Her diabetes was complicated by severe arteriosclerotic heart disease. The arrhythmias that were the eventual cause of death may have been associated with electrolyte imbalance early in her disease, and possibly the terminal arrhythmia was associated with the electrolyte imbalance following her profound diuresis on the third day of hospitalization.

Case 3. An 80 year old woman was brought to the hospital by police ambulance. The patient, who lived alone, had been found unconscious in her room by neighbors. History from her friends and local physician revealed that she had known hypertensive arteriosclerotic heart disease with auricular fibrillation, and that several years before she had been in frank congestive failure. When last seen, one or two days before admission, she had been in fair health.

On admission to the hospital the patient was found to be a cachectic elderly woman, unresponsive to all stimuli. Her blood pressure was unobtainable, her respirations were rapid and deep, and she had the odor of acetone on her breath. Brownish guaiac-positive material was found about her mouth. Her chest was clear, her

heart enlarged 2 cm. to the left of the midclavicular line, and her abdomen not remarkable. Neurologic examination demonstrated extreme flaccidity.

Initial urine obtained by catheterization revealed 4 plus sugar, 4 plus acetone and 2 plus albumin. Her blood sugar was 310 mg.%; carbon dioxide combining power, 5 mEq./L.; nonprotein nitrogen, 30 mg.%. Her stools were slightly guaiac-positive. The hematocrit was 43 vol.%; white blood count, 26,500 cells per cubic millimeter, with a normal differential count. A lumbar puncture was normal. Initial electrocardiogram showed peaked T waves as the only abnormality.

The patient was treated with Solution "A," plus a unit of whole blood, vasopressor agents, and 100 units of regular insulin given intravenously. After six hours of therapy she had received 500 units of regular insulin and a total of 3.5 L. of fluid intravenously. Her blood sugar fell to 210 mg.%, her carbon dioxide combining power rose to 19 mEq./L., and her urine showed 2 plus sugar and 1 plus acetone. She was then hydrated with 5% dextrose in water with potassium added (Solution "B"). An electrocardiogram at that time was normal.

Throughout this period the patient remained comatose. She soon thereafter started to vomit brownish, guaiac-positive material. Her urinary output, which had been minimal (100 c.c. in six hours), fell to 0. After 12 hours she died. Postmortem permission could not be obtained.

Clinical Diagnoses:

1. Diabetic coma (treated).
2. Gastrointestinal bleeding of unknown etiology.
3. Acute renal failure.
4. History of hypertensive arteriosclerotic heart disease.

Comment: It is difficult to decide which of the many possible factors caused the patient's ultimate death. Although she was not in renal failure on admission, it was evident that her kidney status was precarious. Her continued gastrointestinal bleeding as well as the severe diabetic acidosis doubtless contributed to the renal failure. The reëstablishment of chemical balance did nothing to alter the state of consciousness of the patient or the ultimate outcome.

Case 4. A 69 year old housewife was brought to the hospital because of coma of eight to 16 hours' duration. She had known diabetes of two years' duration that was controlled by diet alone. Two weeks prior to admission she had complained of a "sore thigh," polyuria, polydipsia and nocturia. One week later a boil on her right buttock ruptured and continued to drain purulent material up to the time of hospital admission. For several days prior to admission she had been lethargic and had remained in bed throughout the day. On the day prior to admission she was disoriented, and on the morning of admission could not be aroused. Her past history included a partial colectomy for carcinoma of the colon 11 years previously.

On examination at the time of hospital admission the patient was found to be comatose, markedly dehydrated and breathing rapidly. There was no odor of acetone on her breath. Her blood pressure was unobtainable; pulse rate, 160; temperature, 99.8° F. rectally. Heart, lungs and abdomen were negative but for a well functioning colostomy. A draining abscess was found on her right buttock.

Initial urine gave a 4 plus sugar test and 3 plus acetone test. Initial blood sugar was 475 mg.%; carbon dioxide combining power, 14 mEq./L.; nonprotein nitrogen, 101 mg.%. Her white blood count was 14,000 cells per cubic millimeter, with a polymorphonuclear shift to the left. The hematocrit was 44 vol.%. A lumbar punc-

ture was within normal limits. Three blood cultures obtained in the course of her 18-hour hospitalization were negative. The abscess on her buttock grew out hemolytic *Staphylococcus aureus, B. proteus* and *Aerobacter aerogenes.* Initial electrocardiogram showed only a sino-auricular tachycardia.

In the first 10 hours the patient was hydrated with four liters of Solution "A," one pint of whole blood and 500 c.c. of normal saline. She also received continuous Levophed in her hydrating solutions, plus 1,000 units of regular insulin, one-half of it intravenously, the other half subcutaneously. One million units of penicillin were also administered. With this therapy the patient's blood pressure rose to 100/80 mm. of Hg in one hour. Her blood sugar fell to 298 mg.%, and her carbon dioxide combining power rose to 23 mEq./L. The electrocardiogram at the end of this 10-hour period showed some S-T depression and a shifting auricular pacemaker. Electrolytes demonstrated that the serum sodium was elevated to 165 mEq./L. and the serum potassium was depressed to 2.5 mEq./L. She was given Solution "B" (with 45 mEq. of potassium). Her urinary output, which had been minimal at the time of admission, did not improve, and remained at a level of only a few cubic centimeters per hour. With further therapy the patient's blood sugar and carbon dioxide combining power returned to normal, but her temperature rose to 102.6° F. rectally, and her blood pressure became unobtainable again. Eighteen hours after admission she died without recovering consciousness. Postmortem permission was not obtained.

Clinical Diagnoses:

1. Diabetic coma.
2. Acute renal shutdown.
3. Staphylococcal abscess of right buttock.

Comment: This woman probably had her diabetic coma precipitated by the infection on her buttock and was in severe acidosis at home for days. The renal shutdown secondary to the severe acidosis and dehydration was not given sufficient attention. However, despite her minimal output, there never was clinical evidence of edema or congestive changes in the lungs. Her total fluid intake over the 18-hour period was about 6.5 L. Although the hypokalemia at 10 hours may have played a role in her death, it was corrected within one to two hours after it was noted. The rising temperature, not observed in other cases, may have indicated more widespread infection than the abscess on her buttock. This patient might have benefited by the use of the artificial kidney, as reported by Aoyama and Kolff,[47] but whether such measures would have been lifesaving is a moot question.

Discussion

Seventy-three patient admissions for diabetic acidosis have been reviewed in detail and commented on with respect to the cause, course and management of the disease. Several points are worthy of further discussion. Not one of the patients with this complication had a previous record of good diabetic control. Indeed, the 11 patients with multiple admissions in acidosis invariably had very poorly controlled diabetes. Thus, though the role of good control in the prevention of the long-term complications may be a subject for debate, there is no question of its importance in preventing the ever-present danger of diabetic acidosis.

Although it is well known that infections, overeating and the like may lead to a state of acidosis, the role of emotional factors has not been commented on in detail. Many of the patients who were most neglectful in their care had severe personality disorders. The psychiatric evaluation of the 19 year old girl who had nine admissions in severe acidosis was that of a schizoid personality. She was followed by a psychiatrist during several of her hospitalizations, and on at least one occasion it was felt that her omission of insulin was a suicidal gesture during a reactive depression. Difficulties in adjustment among the other patients were not rare, and it is significant that five of the admissions were precipitated by severe alcoholic binges.

The clinical picture of acidosis was usually uncomplicated. Lawrence [45] has commented on several of the more unusual manifestations (i.e., maniacal violence, intense lumbar pain, etc.), but, of these, only acute abdominal pain was observed. The pain disappeared completely within 12 hours of adequate treatment. Although there were several notable exceptions, the patients admitted in coma had lower carbon dioxide combining powers and more marked blood sugar elevation. The level of neither the blood sugar nor the carbon dioxide combining power, however, was related to the ultimate outcome.

In the management of the patients, the early use of large doses of insulin appeared to exert a beneficial effect, although it is impossible to document this fact without controls on lower doses. For fluid replacement, hypotonic solutions were utilized. It was felt that these provided flexibility in the therapeutic régime, and that one could approach the quantitative replacement of water and electrolyte losses.

For initial hydration, one to three liters of the hypotonic solution containing sodium, 100 mEq./L., chloride, 60 mEq./L., and lactate, 40 mEq./L., were used. If there was sufficient improvement, as seen in the blood and urinary sugar, 5% glucose was added after from four to six hours. If improvement in blood and urinary sugar had not occurred after three liters of hypotonic solution, saline often was administered, depending upon the electrolyte measurements. The total water requirement intravenously rarely exceeds from 5 to 7 liters and the total sodium needed is approximately 350 to 500 mEq. during the initial 24 hours of therapy for adults. These figures, however, can serve only as a rough guide, and each case must be individualized. With the use of hypotonic solutions, hyponatremia is a potential danger,[10] but it did not prove to be a problem. Previous experience suggested that errors in fluid administration were more often in overtreating than in undertreating.

No attempt was made to replace the total potassium losses intravenously during the first 24 hours. Less than half the patients received intravenous potassium, and no cases of severe hypokalemia were observed. Potassium by mouth was added between hours six to 12 when it could be tolerated by

the patient. Serum phosphorus levels paralleled the potassium levels, although the falls were often more marked. In one instance the initial phosphorus of 13.6 mg.% fell to 0.57 mg.% after nine hours of therapy. In the limited number of patients whose phosphorus was followed there was no correlation between the clinical state and the blood phosphorus level.

The dangers of continuous catheterization were clearly indicated in this study. The high infection rate and the possible relationship of one death have been commented upon. The mortality rate (5.5%) at a large municipal hospital compares favorably with those recorded in the literature.[46] All the deaths were in the older age group, in patients with known complications. It is conceivable, though, that even these types of fatalities may be avoided in the future with proper use of antibiotics and catheters, more careful attention to electrolytes and insulin, and, in selected cases, the use of the artificial kidney.[47]

Summary

1. The etiology, course and management of 73 patient admissions for diabetic acidosis in a municipal hospital were reviewed in detail.

2. The role of emotional disturbances, as well as infections, in precipitating the acidosis was stressed. Not one of the known diabetics had previously been in good control.

3. The symptoms and signs on hospital admission were reviewed and compared to previously reported series.

4. The early use of large doses of insulin was perhaps the most significant therapeutic measure.

5. With the use of hypotonic solutions, and with careful assessment of potassium needs of the patients, few problems in electrolyte replacement were encountered.

6. Early use of long-acting insulin and early ambulation led to shortened hospitalization.

7. The dangers of indwelling catheters and the use of antibiotics only for specific infections were discussed.

8. The four deaths (mortality rate, 5.5%) occurred in patients 65 and over, all of whom had other complications.

Summario in Interlingua

Esseva revistate in detalio le etiologia, le curso, e le tractamento de acidosis diabetic in 73 patientes admittite a un hospital municipal. Esseva constatate que disturbationes emotional si ben como infectiones esseva causas precipitatori del acidosis. Non un sol del gruppo de cognoscitemente diabetic patientes habeva dominio del morbo. Le aspecto clinic del acidosis in le casos del presente serie esseva usualmente non-complicate, excepte le presentia de acute dolores abdominal in plures del patientes. Le dolores dispareva completemente intra 12 horas post le initiation de un forma adequate de tractamento.

Quanto al tractamento del diabete, le uso precoce de large doses de insulina pareva exercer un effecto benefic. Como reimplaciamento de liquido esseva usate

initialmente un solution hypotonic continente natrium, 100 mEq/L, chloruro, 60 mEq/L, e lactato, 40 mEq/L. Le precoce introduction de insulina a action prolongate e de ambulation resultava in un reduction del periodo de hospitalisation. Le periculo de continue catheterisationes e le importantia del uso de antibioticos pro infectiones specific es discutite. Le series includeva quatro casos mortal, un mortalitate de 5.5%. Omne iste mortes occurreva in patientes de plus que 65 annos de etate qui omnes habeva altere complicationes.

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COMBINED PRIMARY AND SECONDARY HYPERPARATHYROIDISM: TWO CASE REPORTS AND A REVIEW *

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Although the literature on hyperparathyroidism is extensive, there are few case reports of functioning parathyroid adenoma occurring simultaneously with secondary hyperplasia of the parathyroid gland.[2, 3, 4, 5, 6] Albright and Reifenstein discussed only one such case when they wrote their classic monograph[1] on metabolic bone disease. Most of the reported cases have not been carefully studied ante mortem, and this is true of the two reported below. Secondary hyperplasia following the removal of a functioning adenoma where there has been irreversible damage to the kidneys has often been reported[27, 50, 57, 77, 78, 79] and is not hard to understand. When the two lesions occur simultaneously, the phenomenon is somewhat of a paradox and more difficult to explain.

The two cases reported here were found in a survey of postmortem examinations over a 10 year period at Montefiore Hospital.

Case Reports

Case 1. A 59 year old white married female with four Montefiore Hospital admissions between 1953 and 1955 was first told of hypertension in 1947. In early 1953 she noted anorexia, weakness, fatigue, loss of weight, dyspnea, orthopnea and urinary frequency. She was admitted to Montefiore Hospital on July 3, 1953, for progression of these complaints. Physical examination showed hypertension (215/160 mm. of Hg) and evidence of severe right- and left-sided heart failure. Eyegrounds showed retinal arterial changes of grade II, and the heart was enlarged to the anterior axillary line.

Laboratory Findings: An electrocardiogram was consistent with left ventricular hypertrophy. Chest x-ray showed a large heart. A hemogram was normal. Urine: specific gravity, 1.010; albumin, 1 plus; some epithelial cells, and occasional clumps of white blood cells. Fasting blood sugar, 95 mg.%; blood urea nitrogen, 58 mg.%.

The patient responded to treatment with a low salt diet, digitalis and mercurial diuretics and was discharged on August 3, 1953. She was followed in the outpatient department, where paroxysmal atrial fibrillation and a questionable nodule in the right upper lobe of the thyroid were noted.

The patient was re-admitted for diagnostic study in October, 1953. An I^{131} uptake was 39% in 24 hours, and she was considered to be euthyroid. The thoracic cage was mildly demineralized on x-ray. Skull films and esophagram were normal. On a Fishberg concentration test the overnight collection had a specific gravity of

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1.002, and the maximal concentration of any specimen was 1.006. All urine specimens had 3 plus to 4 plus albumin, and the standard and maximal clearances of urea were 10% and 9% of average normal function, respectively. Treatment with Raudixin and Apresoline was started.

Nausea and vomiting precipitated the third Montefiore Hospital admission, in September, 1954. At that time the blood urea nitrogen was 70.6 mg.%; creatinine, 7.1 mg.%; sodium, 132 mEq./L.; potassium, 3.5 mEq./L.; carbon dioxide content, 22.6 mEq./L.; chlorides, 96 mEq./L.; calcium, 10.5 mg.%; inorganic phosphate, 6.1 mg.%. Hemoglobin, 11.5 gm. Regitine test, negative.

The patient responded to symptomatic treatment and was discharged on September 24, 1954. Progressive weakness, loss of appetite and severe epistaxis prompted her final admission, on October 22, 1955. Blood pressure was 180/100 mm. of Hg; pulse, 72 and irregular; temperature, normal; respiration, 24. Fundi were unchanged. There was some periorbital edema. The lungs were clear. The heart was enlarged to the anterior axillary line; A_2 was greater than P_2; there was a soft, grade II apical systolic murmur. One plus pitting ankle edema was present. The neurologic examination was negative.

Laboratory Findings: Hemoglobin, 8 gm.%; blood urea nitrogen, 97 mg.%; creatinine, 7.2 mg.%; sodium, 132 mEq./L.; potassium, 3.9 mEq./L.; carbon dioxide content, 14.9 mEq./L.; chloride, 94 mEq./L.; calcium, 11.0 mg.%; inorganic phosphorus, 8.3 mg.%; alkaline phosphatase, 18.2 Bodansky units. X-rays of the skull showed cystic changes. The remainder of the bones were generally demineralized, and there were areas of subperiosteal resorption of the bone. The lamina dura was not seen in x-rays of the mandible. An increase in density of the right renal shadow suggested nephrocalcinosis.

Hospital Course: Deterioration was progressive despite treatment with parenteral fluids and packed red cells. Vomiting and abdominal distention were a persistent feature. The patient died on November 13, 1955. The clinical impression was chronic pyelonephritis with secondary hypertensive cardiovascular disease, hyperparathyroidism and uremia.

Necropsy revealed a well developed, well nourished white female. The kidneys weighed 65 and 75 gm. respectively. There was gross scarring of the renal parenchyma, with some loss of distinction of cortical striations and the cortical medullary junction. There was marked accentuation of the arcuate arteries. The pelves and calyces were not remarkable. Four parathyroid glands were found, three of which were moderately large, tan and somewhat lobulated. The fourth gland was much larger than the rest, measuring 1.0 by 1.5 cm. in greatest diameter, but it was also tan in color. The heart weighed 575 gm., and the left ventricle was hypertrophied. On microscopic examination there was marked renal arterial and arteriolar sclerosis, with extensive fibrous scars throughout the renal parenchyma. The majority of the glomeruli were partially or completely fibrotic, and the tubules showed degeneration, atrophy, regeneration and marked dilatation. There was also a diffuse lymphocytic infiltration. No calcium deposits were seen. The largest parathyroid contained no significant fat. The cells were regular in size and shape, and were largely chief cells, but there were islands of wasserhelle cells and oxyphil cells (figure 1). The remaining glands contained a decreased amount of fat, and the cells were normal-appearing chief cells (figure 2). There was evidence of bone resorption, with many trabeculae containing cystic spaces. In addition, other trabeculae showed evidence of osteoid formation with calcification. Pathologic diagnosis was: renal arterial and arteriolar sclerosis, left ventricular hypertrophy, parathyroid chief cell adenoma, secondary parathyroid hyperplasia, osteitis fibrosa cystica.

Case 2. A 58 year old white male was admitted to Montefiore Hospital on December 27, 1952, because of mental confusion, restlessness, occipital headaches and

weakness of the left leg of several weeks' duration. Two months prior to admission a triple phosphate calculus had been removed from the left kidney at another hospital. The pain in the left flank had disappeared promptly at that time, but symptoms of "Parkinsonism" were noted for the first time postoperatively. Poor appetite and generalized weakness persisted from the time of operation until the onset of the complaints and findings noted above. One day prior to admission a neurologist had

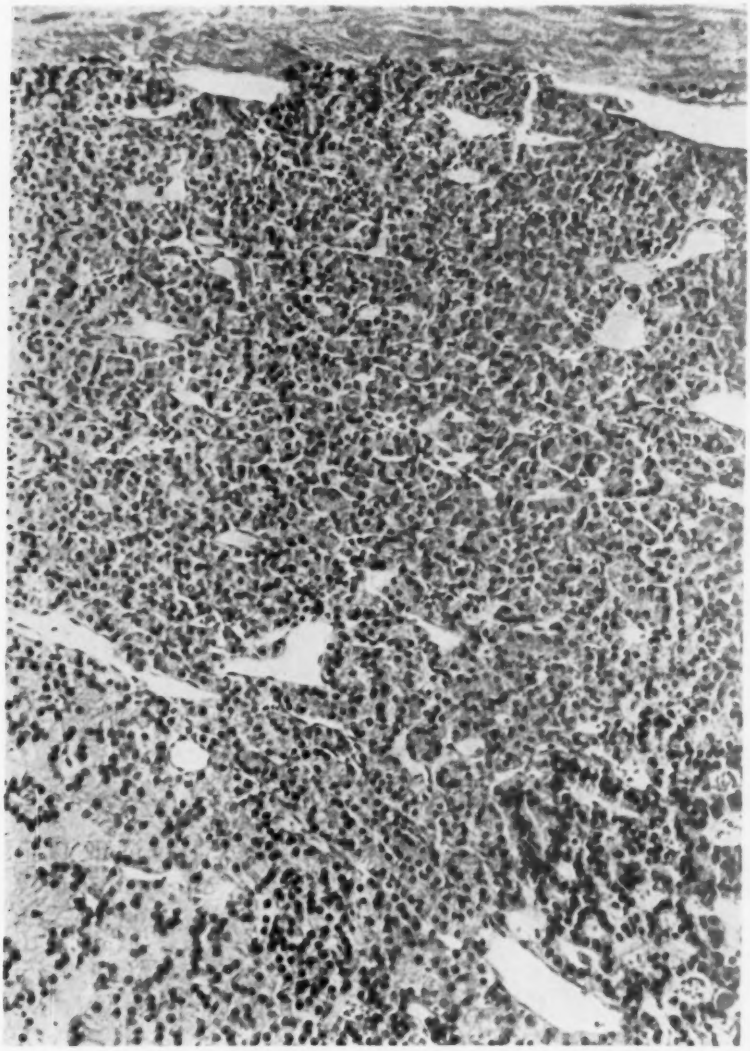

FIG. 1. *Case 1.* Parathyroid adenoma with well developed acinar structure in some foci. Most cells represent chief cells, some of which have clear cytoplasm. × 240

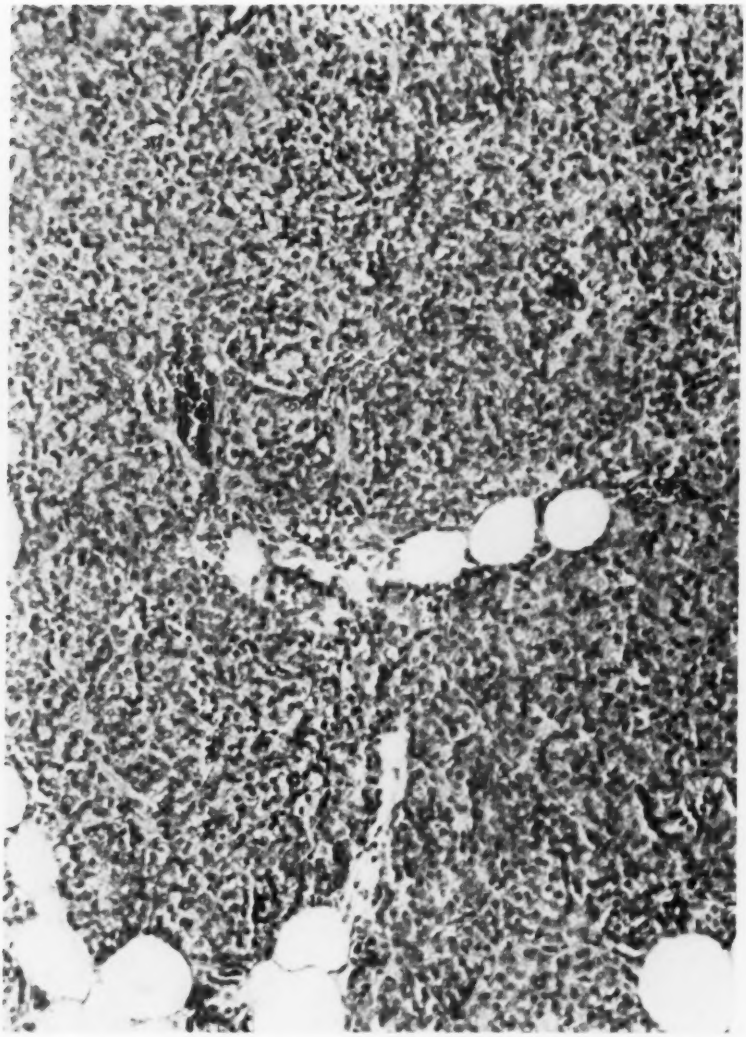

FIG. 2. *Case 1.* Secondary parathyroid hyperplasia, showing decreased amount of fat. The cells are largely active chief cells. ×240

examined the patient and found a left hemiparesis. Past history was not remarkable except for a fracture of the left arm in 1950.

Physical examination on admission showed: temperature 98° F.; pulse 92; respiration, 20; blood pressure, 180/98 mm. of Hg. The patient appeared to be chronically ill and slightly confused. There was bilateral nasal blurring of the optic discs but no definite papilledema. A systolic murmur was heard over the precordium. No masses were palpable in the neck. Neurologic examination: Positive findings

included mental confusion, left hemiparesis, increased muscle tone in all extremities, and active reflexes except for absent superficial abdominals bilaterally. Bilateral Babinski's responses were present, and there was a questionable sensory defect in the left hand.

Laboratory Data: Hemoglobin, 13 gm.; white blood count, 8,100 per milliliter; red blood count, 4,390,000 per milliliter. Urine: specific gravity 1.008; albumin, negative; glucose, negative; microscopic: many white blood cells. Spinal tap: crystal

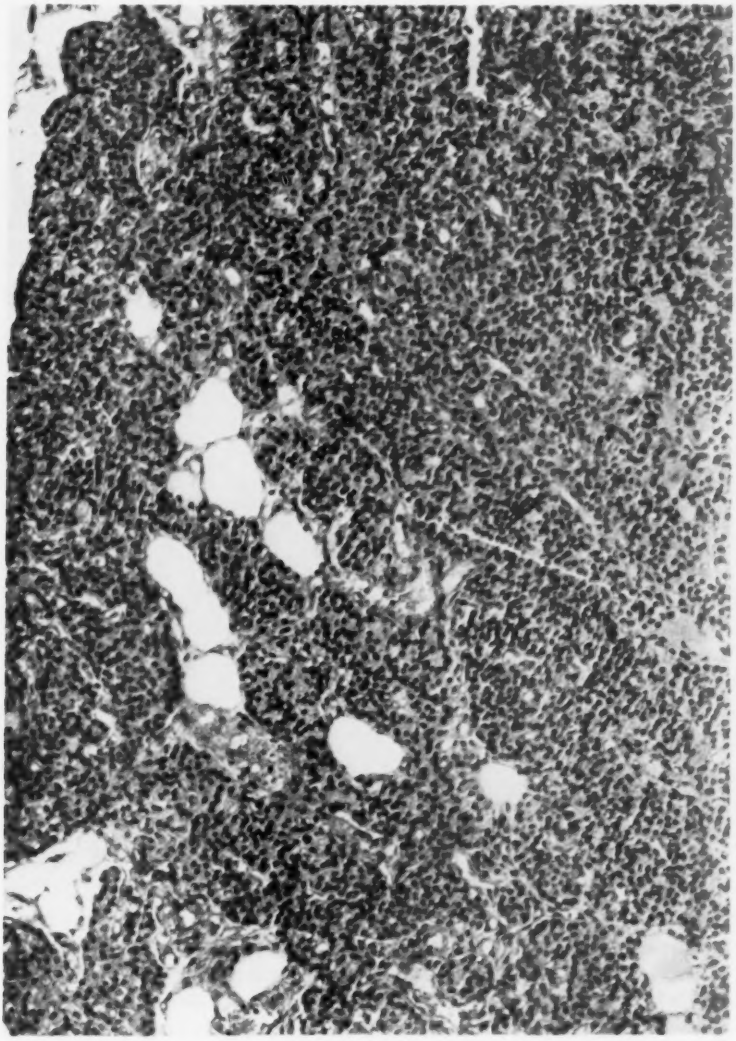

FIG. 3. *Case 2.* Secondary parathyroid hyperplasia with increased cellularity and decreased fat. Most of the cells are chief cells. ×240

FIG. 4. *Case 2.* Parathyroid adenoma with poorly formed acinar structure and prominent fibrous stroma. × 240

clear fluid under normal pressure. Sugar, 71 mg.%; total protein, 40 mg.%. Serologic reaction and culture, negative. Chest x-ray was within normal limits. Skull films showed some demineralization of the sella. X-rays of the lumbar spine showed some demineralization.

Hospital Course: The patient remained afebrile, but his condition gradually declined, his mental state degenerating into complete disorientation and stupor. A

few moments before death he became cyanotic, his blood pressure fell, and the pupils dilated and became fixed. No papilledema was noted at that time. The patient died quietly on January 6, 1953. The clinical impressions were: (1) right frontoparietal tumor with extension to the left side; (2) bilateral brain stem metastases from an unknown primary neoplasm, or (3) a midbrain vascular lesion. Parkinsonism was a subsidiary diagnosis.

Necropsy revealed a well developed, poorly nourished white male. Four moderately enlarged parathyroid glands were identified. Adjoining one of the glands was a large, yellow-tan nodule measuring 2.5 cm. in greatest diameter. The kidneys weighed 170 and 180 gm. The surfaces of the kidneys were smooth except for one small scar. The cortices and medullae were intact and not remarkable. The pelves and calyces were also grossly not remarkable. No bone changes were noted. The heart weighed 410 gm. and the left ventricle was hypertrophied. The lungs were congested. The brain was grossly normal. On microscopic examination, the parathyroid glands showed cellular hyperplasia and diminished fat. Most of the cellular elements were normal-appearing chief cells (figure 3). The large nodule contained no significant fat and was composed of closely packed sheets of normal-appearing chief cells (figure 4). The kidneys showed widespread calcification, most prominently in the glomeruli and tubules. There were also small subcapsular fibrous scars. There was mild generalized osteoporosis, with small foci of myelofibrosis. Foci of bone resorption with osteoclasts were present, but there were no areas of cyst formation. The brain showed necrobiosis of cells in the substantia nigra and the globus pallidus. Pathologic diagnosis: parathyroid chief cell adenoma, secondary parathyroid hyperplasia, nephrocalcinosis, left ventricular hypertrophy, necrobiosis of the substantia nigra and the globus pallidus.

Discussion

Each of these two cases represents one of the two ways that simultaneous primary and secondary hyperparathyroidism may occur. In the first case, secondary parathyroid hyperplasia and hyperparathyroidism are seen as the outcome of renal disease with uremia.[9, 11, 54, 59] The adenoma was either an incidental occurrence or, as some suggest,[1, 4, 7] a neoplastic response to the nonspecific stimulation to hyperplasia. The high serum calcium levels in the presence of hyperphosphatemia and acidosis, and the presence and predominance of chief cells in the adenoma,[5, 8, 32] favor the presumption that the adenoma was secreting actively. In the second case, the absence of primary renal disease argues strongly for the sequence of a primary hyperfunctioning parathyroid adenoma producing nephrocalcinosis and renal insufficiency, with secondary hyperplasia and hyperfunction of the remainder of the parathyroid glands.

Cases reported in the literature are of these two general types.

In 1937 Kalbfleisch[2] reported a case of multiple endocrine adenomata including a chromophobe tumor of the pituitary, five islet cell tumors of the pancreas, and a chief cell adenoma of one parathyroid gland with enlargement ("pea sized"), hyperplasia, and loss of fatty stroma in the remaining three glands. A left renal calculus was present, but the kidneys were otherwise normal. No blood calcium determinations were reported.

The case of Downs and Scott (1941)[3] was cited by Albright and Reifen-

stein [1] as a convincing example of primary parathyroid adenoma with generalized bony demineralization, nephrocalcinosis, renal failure and secondary hyperplasia of the three remaining nonadenomatous parathyroid glands. Serum calciums were 7.5 and 7.6 mg.%, and the serum inorganic phosphorus was 4.1 and 5.8 mg.%, respectively. At the postmortem examination there was much cystic change in the adenoma, which may explain both the low serum calcium and the secondary hyperplasia; i.e., if the cystic

TABLE 1

Case	Ref.	Parathyroid Pathology	Kidneys	Bones	BUN mg. %	CO_2 vol. %	Ca mg. %	P mg. %
1. Kalbfleisch,[2] 1937		Chief cell adenoma, hyperplasia with loss of interstitial fat	Renal calculi	Decalcif.				
2. Downs and Scott,[3] 1941		Chief cell adenoma, secondary hyperplasia	Nephrocalcinosis	Decalcif.	Up		7.5 7.6	4.1 5.8
3. Soffer and Cohen,[4] 1943		1/30/38—4 enl. glands at surg.; 2 removed. Chief cell adenoma in one, some hyperplasia of oxyphilic and clear cells in the other. 10/36—1 and ½ glands removed; hyperplasia of all elements	Renal function poor; bladder calculi		29 13	50.5	14.0 13.1	3.3 3.1
4. Lee et al.,[5] 1955	(case 6)	Chief cell adenoma 3 cm. × 2.5 cm. 3 enl. glands, 1.5 × 0.5 cm. with secondary hyperplasia	Nephrocalcinosis	Osteitis fibrosa	 165		10.5 11.1 11.3 9.2	7.2 11.2 9.4 16.9
5. Bogdonoff et al.,[6] 1956	(case 17)	Adenoma and secondary hyperplasia	Nephrocalcinosis		224		10.8 10.5	8.8
6. Case 1		Adenoma and secondary hyperplasia	Intrinsic renal dis. (chr. pyelonephritis)	Osteitis fibrosa	70.6 49 97.4 93.6		10.5 11.1 11.0 10.6	6.1 4.8 8.3 6.3
7. Case 2		Adenoma and secondary hyperplasia	Nephrocalcinosis, renal calculi	Moderate demineral.				

degeneration took place after the development of nephrocalcinosis with uremia, there would not be enough circulating parathormone to maintain the blood calcium in the face of acidosis and a rising serum phosphorus. The resulting low calcium would then, according to traditional theory, result in secondary parathyroid hyperplasia.

Soffer and Cohen's case [4] was that of a 42 year old white male with an epulis of the lower jaw, generalized bony demineralization and cystic changes in the bones, and bladder calculi. The blood calcium was 14.0 mg.%; inorganic phosphorus, 3.3 mg.%; blood urea nitrogen, 29 mg.%. At operation, all four parathyroid glands were enlarged. Two were removed, and

a chief cell adenoma was found in one gland, with some hyperplasia of the oxyphil and clear cells in the other. Fifteen months later the blood calcium was 13.1 mg.%, inorganic phosphorus, 3.1 mg.%. The specific gravity of the urine was fixed at 1.012, the urea clearance was 43% of normal, and the phenolsulfonphthalein test showed 15% excretion of dye in four hours. The remainder of one gland and one-half of a second gland were removed. Microscopic examination of these specimens revealed diffuse hyperplasia of all cell types. The authors believe the sequence of events to be a functioning parathyroid adenoma producing a bladder stone which, in turn, caused a chronic nephritis and secondary parathyroid hyperplasia. This case is unusual in that secondary parathyroid hyperplasia was found in the absence of hypocalcemia, hyperphosphatemia, marked azotemia or acidosis (CO_2 was 50.5 vol.%).

A well documented case, similar to the one reported by Downs and Scott,[3] is described by Lee et al.[5] They note that since, in the phosphorus retention of severe renal disease leading to secondary hyperparathyroidism, the serum calcium usually falls, the elevated serum calcium (11 mg.%) in this case supports the conclusion that the functioning adenoma preceded the renal disease. They do not feel that the two other cases reported by them of hyperplasia and adenoma are bona fide examples of combined primary and secondary hyperparathyroidism.[28]

A third case of a functioning parathyroid adenoma leading to nephrocalcinosis, renal failure and secondary parathyroid hyperplasia was reported by Bogdonoff et al.[6] Here, also, the serum calcium level was higher than that usually seen in simple secondary hyperplasia.

The occurrence of parathyroid adenoma and secondary hyperplasia is probably more common than the scanty reports in the literature would indicate. One author, for example, notes in a personal communication that he has seen three such cases in the presence of severe intrinsic renal disease.[7]

Castleman,[8, 9] Black [32] and others [10, 13] have outlined the criteria for diagnosis and the problems confronting the pathologist when describing and interpreting pathologic alterations of the parathyroid. In brief, all of the various cell types of the parathyroid gland may be represented in a functioning adenoma. However, adenomas consisting of eosinophilic cells alone do not secrete excess parathormone. The intensity of function is independent of cell type or size of the adenoma. Multiple functioning adenomas are rare, but have a similarity to secondary hyperplasia with adenomatous change and must be carefully distinguished.[29] The diffuse wasserhelle hyperplasia, a cause of primary hyperparathyroidism, is easily separated from the more heterogeneous secondary variety. Also, adenomas have not been reported in the presence of such primary hyperplasia,[60] with one possible exception.[79]

Causes of secondary hyperplasia of the parathyroid gland are numerous [1, 11, 14, 15, 38, 42, 56, 58] and are usually, although not always,[12, 14, 47, 58] correlated with a factor lowering the serum calcium. Bergstrand,[54] MacCallum [55] and

Pappenheimer and Wilens[11] related renal insufficiency to parathyroid hyperfunction and secondary hyperplasia. Bone changes in renal insufficiency are those of failure of calcification of osteoid (as in rickets), as well as osteitis fibrosa cystica.[54] Snapper[76] reviewed the evidence favoring acidosis as a cause of the osseous pathologic changes of renal disease. Stanbury[63] supports parathyroid hyperfunction as a cause of the bony lesions of renal disease. Much work has been done to implicate phosphorus retention as a cause of increased parathyroid activity,[12, 13, 14, 18, 19, 20, 21, 22, 47, 51] but even to the present, authorities are unconvinced, a decrease in the ionized blood calcium remaining the only proved stimulus to parathyroid hyperfunction.[23, 24, 25, 61, 63] Indeed, Ham et al.[64] fed vitamin D-deficient rats on a diet high in calcium and phosphorus and obtained high serum levels of both calcium and phosphorus, but no increase in the weight of the parathyroids. Parathyroid hypertrophy was found when the diet was either high or low in phosphorus, but uniformly low in calcium with corresponding changes in blood serum levels. No such experiment has been done in the presence of uremia.

Since the initial investigations of Albright et al.[1, 33] into parathyroid physiology many workers have offered evidence modifying the original theory that one hormone and the effect upon one target organ were responsible for the entire abnormal physiology of hyperparathyroidism, with blood and bone changes dependent upon the consequences of decreased tubular reabsorption of phosphorus on a fixed equilibrium product of calcium and phosphate ions in the body fluids.[14, 26, 47]

A variety of parathyroid functions have been proposed, e.g., calcium mobilization directly from bone,[23, 26] growth inhibition,[36] promotion of diuresis,[15] elevation of blood pressure in the rat and in man,[34, 68] mobilization of mucopolysaccharide,[37, 45, 46] mobilization of citrate,[39, 40] regulation of lactation,[47] regulation of magnesium metabolism,[61] and, as mentioned above, inhibition of phosphate resorption by the kidney tubule. Fractions of the crude hormone have been isolated, with claims of varying validity that one or another property is dominant in a particular fraction.[15, 41] Some suggest that there are two principal hormones secreted by the gland, one stimulated by an elevated serum phosphorus, the other by a lowered serum calcium.[14, 16, 47]

The cases reported here cannot be readily explained by the available data. It is clear, however, that secondary hyperplasia of the parathyroids, a functioning parathyroid adenoma, and a normal or elevated serum calcium may all be present in the same individual at the same time. It also seems reasonable to conclude that, in cases 2, 4, 5 and 7, where the adenoma was the first event in the pathologic sequence, the secondary parathyroid hyperplasia developed without there ever having been a significant lowering of the serum calcium.

The following explanations are suggested: (1) that the serum calcium, while not low, is below the threshold to which the gland has been "accli-

mated" under the influence of the parathyroid adenoma, and it is therefore responding to a "relative" hypocalcemia induced by the renal failure and acidosis; (2) that the fluctuating excretory function of these adenomas [32, 69] in the presence of uremia may have resulted in periods of hypocalcemia, with secondary hyperplasia of the parathyroid gland which persisted because of some acquired autonomy, rather than a continued stimulus to hyperfunction; (3) that under usual circumstances a low serum calcium is the immediate stimulus of secondary hyperplasia, but in the presence of an elevated or normal blood calcium, phosphatemia or some other factor in the uremic acts as the stimulus; (4) that under certain circumstances the high serum calcium level may not represent a correspondingly high level of ionized calcium. Although studies by McLean and Hastings [30, 31] showed the ionized calcium to be a constant and predictable proportion of the total blood calcium, even in cases of hyperparathyroidism, more recent studies by a new technic developed by Rose [74] do not confirm this. Citrate has been implicated as lowering the ionic calcium, since the blood citrate level is elevated in both uremia [62] (animal experiments have demonstrated an important role for the kidney in citrate utilization [70, 71]), and parathyroid hyperfunction.[39, 40] Fanconi and Rose [73] have shown that, with the blood urea nitrogen in the neighborhood of 100 mg.%, the "complexed" calcium—that is, the calcium bound to citrate and perhaps to other inorganic acids [72]—is elevated and accounts for some of the serum calcium previously thought to be entirely ionized. Other phenomena support this last view, in that they too may be best explained by an occult decrease in ionic calcium—e.g., Yendt et al.[67] noted failure of calcification of rachitic rat osteoid with ultrafiltered uremic serum in which the calcium-phosphate ionization product was less than 55, whereas similarly treated serum from normal subjects calcified osteoid at ionization products of 30. Also, suggestive evidence of parathyroid hyperfunction in renal disease (marked increase in the phosphate/creatinine clearance ratio) may occur before any change is seen in serum calcium or phosphorus.[66] In an excellent review, Nordin [61] notes that the serum calcium falls in many cases of uremia before there is any significant increase in the serum phosphorus.

More careful antemortem study of cases such as these, with specialized and newer technics for the determination of calcium compounds in the blood,[23, 48, 49, 74, 75] is to be hoped for.

Summary

1. Two cases of combined primary and secondary hyperparathyroidism are reported, and the literature is reviewed.

2. This entity may be suspected in uremic patients with bony demineralization and a normal or elevated serum calcium.

3. Theoretic explanations are offered concerning the etiology of this condition.

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SUMMARIO IN INTERLINGUA

Le scrutinio de un collection decenne de studios necroptic a un grande hospital voluntari discoperiva duo casos clarmente characterisate per le presentia de tanto un adenoma cellular principal como etiam de un hyperplasia secundari del glandula parathyroide. Le patiente in un del casos esseva un femina de racia blanc de 59 annos de etate con hypertensive morbo cardiovascular e pyelonephritis chronic qui moriva in uremia con generalisate dismineralisation ossee e alterationes cystic del cranio. Ben que illa habeva uremia con acidosis e elevate nivellos seral de phosphoro, su contento seral de calcium esseva uniformemente normal o elevate (10 a 11 mg%). Le patiente in le secunde caso esseva un masculo de racia blanc de 58 annos de etate, admittite al hospital con confusion mental, disquietude, mal de capite occipital, e debilitate del gamba sinistre. Determinationes del nivellos seral de calcium e phosphoro non esseva effectuate, sed radiogrammas del cranio e del spina lumbar revelava dismineralisation ossee. Le patiente deveniva stuporose e postea comatose, e ille moriva post sex septimanas. Le constatationes pathologic esseva un adenoma parathyroide del typo de cellula principal, secundari hyperplasia parathyroide, e nephrocalcinosis diffuse. Esseva trovate nulle indicio de primari morbo renal.

Cinque casos additional de ille genere esseva trovate in le litteratura. Es presentate un revista del characteristicas clinic e pathologic de iste casos. Illos forma duo gruppos. In le prime il ha disfallimento renal secundari a nephrocalcinosis; in le secunde, morbo renal primari. In ambes, le presentia simultanee de adenoma de cellula principal e de hyperplasia parathyroide secundari esseva associate con nivellos normal o elevate del calcium in le sero.

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STUDIES OF CHOLINESTERASE ACTIVITY. V. SERUM CHOLINESTERASE IN PATIENTS WITH CARCINOMA *†

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Although several reports have described a depression of serum cholinesterase activity in patients with neoplastic disease, a clear correlation has not been established between the quantitative level of enzyme activity, the site of origin and degree of spread of the tumor, the function of the liver and the clinical status of the individual patient. In the absence of a satisfactory explanation of this phenomenon, further investigations of the metabolism of the enzyme in the tumor state seemed warranted.

Serum cholinesterase (pseudocholinesterase) is manufactured by the liver [1-5] and found in serum, plasma, pancreas, brain and certain other body tissues.[6-9] It is distinctly different biochemically from acetylcholinesterase, which is found in neuromuscular and other body tissues and functions in the conduction of the nerve impulse.[9-14] A consistent range of values has been found for normal healthy subjects,[15] although a familial low serum cholinesterase activity has been described as a very rare occurrence in otherwise normal persons, probably due to the presence of an atypical variety of the enzyme in their sera.[16]

It has been shown that serum cholinesterase activity is depressed in various disorders of the liver, such as hepatitis, cirrhosis and benign extrahepatic obstruction of long standing.[5, 17-21] It has also been found to be depressed in severe nutritional deficiency states,[4, 17, 22-24] severe infection,[23] certain mental disorders,[25] and in occasional patients with diffuse mesenchymal disease.[26] In many instances there was no evidence of morphologic parenchymal liver damage or aberration of the usual tests of liver function. In addition, women during normal pregnancy and their newborn offspring have been shown to have low serum cholinesterase activity.[27]

Certain chemical agents acting in vivo or in vitro have the capacity to lower the activity of the enzyme. Among these have been several organic phosphoric nerve gases and insecticides,[2, 28-41] various prostigmine-like anticholinesterases,[42-50] certain muscle-paralyzing anesthetic adjuvants,[51-55] many opiates, barbiturates and other sedatives,[56-58] quinidine [59] and a variety of other drugs.[60-66]

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Elevations of serum cholinesterase have been noted in nephrosis,[2-4, 67] in some patients with essential hypertension,[67, 68] and in certain varieties of severe anxiety states.[69, 70] The administration of parenteral cholinesterase has not proved to be effective in reversing the shock of human myocardial infarction,[71] although it did restore normal blood pressure in hyperthyroid dogs suffering from neurogenic shock.[72] Despite the information cited above, the actual physiologic function of serum cholinesterase is not clearly understood at this time.

It has been stated that serum cholinesterase is synthesized by the liver in parallel with albumin.[67] Several authors have reported coincident depression of serum cholinesterase and serum albumin in both benign and malignant disease [4, 15, 22, 24] inferring that the fall in enzyme activity was a pari passu manifestation of deficient protein synthesis in the debilitated patient. In a group of patients with neoplastic disease, it was felt that the depression of enzyme activity noted was due to debilitation, and similar low levels of serum cholinesterase were noted in debilitated patients without neoplastic disorder.[22] Depression of serum cholinesterase activity has been recorded in patients with tumor metastatic in the liver.[2, 74] The longer the period of biliary obstruction, the lower were the enzyme levels in these patients. An apparent relationship between serum cholinesterase activity and tumor in a small series of patients with extrahepatic biliary obstruction has also been noted.[75] The mean duration of the obstruction in those patients with malignant disease was 69 days, as compared with 29 days for those with benign disease. It was suggested that increased hepatic parenchymal damage, and possibly the general nutritional status, might have contributed to the depression of the enzyme in these cases.

On the other hand, a series of patients reported in 1937,[73] including a small number with neoplasm, showed variations in serum cholinesterase activity which did not correlate with the type or severity of the disease process or the general nutritional status of the individual cases. In addition, Fremont-Smith [76] noted depression of serum cholinesterase in patients with advanced neoplastic disease but without cachexia. Another group of his patients with both neoplasm and cachexia had still lower enzyme activity. This observation was one of the first suggesting that neoplasm per se might influence cholinesterase activity in human serum.

Additional observations confirming low serum cholinesterase activity in patients with tumor were made by Levine and Hoyt,[77] who observed significantly low activity of the enzyme in a series of 26 patients with tumor. Mollander et al.[78] described low enzyme activity in a group of 20 patients with carcinoma and 13 with lymphoma. Four of their patients exhibited a more pronounced depression of the enzyme in association with extrahepatic obstruction by tumor tissue. In some cases the only abnormality of liver function noted was a low serum cholinesterase activity.

Another series of 21 patients with carcinoma and 53 with lymphoma and

leukemia indicated a significant lowering of the activity of the enzyme, which appeared to increase as tumor spread.[75, 79] The most striking results were noted in the carcinoma group. Several cases without histologic evidence of hepatic involvement by neoplasm had a low cholinesterase.

Because of the possibility that the fall in serum cholinesterase activity might reflect the enzyme-metabolic effect of tumor tissue, as well as being of some prognostic use in the evaluation of the tumor patient, it was felt that further exploration of this phenomenon was indicated.

Method

All of the 208 patients in this series had carcinoma at the time of study. The site of the primary lesion was determined by histologic evidence. Patients with any major concurrent disease, significant essential hypertension, pregnancy or hepatic disease (other than that related to tumor involvement) were excluded. Laboratory studies were not performed during the activity of drugs known to depress serum cholinesterase in vivo.

Each patient was personally examined by at least one of three of the authors, the examination including the taking of a detailed history, physical examination, follow-up examinations, and a complete review of laboratory and roentgenologic data. Laboratory tests performed were as follows:

1. Serum cholinesterase activity by the method of de la Huerga et al.[15, 80]
   Normal range: 150 to 305 units per cubic centimeter.
2. Serum albumin by the method of Kingsley.[81]
   Normal values: 3.8 or more gm. per 100 c.c.
3. Serum globulin by the method of Kingsley.[81]
   Normal range: 2.0 to 3.5 gm. per 100 c.c.
4. Serum total cholesterol by the method of Zak.[82]
   Normal range: 150 to 300 mg.%.
5. Serum cholesterol esters by the method of Zak.[82]
   Normal range (expressed as percentage of total): 65 to 75%.
6. Serum alkaline phosphatase activity by the method of Roe and Whitmore.[83]
   Normal values: less than 5.0 Bodansky units per cubic centimeter.
7. Serum total bilirubin by the method of Malloy and Evelyn.[84]
   Normal values: up to and including 1.0 mg.%.
8. Serum thymol turbidity by the method of Shank and Hoaglund.[85]
   Normal values: less than 4.0 units per cubic centimeter.
9. Hematocrit by the method of Wintrobe.
   Normal range: above 35%.
10. Erythrocyte sedimentation rate by the method of Westergren.
    Normal range: up to 39 mm. per hour.

The *degree of spread* of neoplasm was based on evaluation of all available clinical and laboratory data. However, information derived from such

observations as general clinical condition and history was given little weight unless confirmed by objective findings. The laboratory tests previously referred to were not considered in the evaluation of the degree of spread of carcinoma, inasmuch as they represented the parameters being analyzed in the over-all study of these patients.

Among those criteria most useful in establishing the degree of spread of tumor were the following:

1. *Physical examination:* Enlarged, firm lymph nodes; hepatomegaly, particularly if firm, nodular or massive; irregular abdominal or pelvic masses in nonirradiated cases; skin masses.
2. *Radiologic evidence:* Bone lesions, pulmonary lesions, and evidence of space-filling defects in hollow viscera.
3. *Surgical procedures:* Biopsy of lymph node, skin, liver and other tumor mass; exploration of the abdominal, thoracic or pelvic cavities.
4. *Postmortem examination.*

On the basis of the combined information, patients were then classified as follows:

Group I: *Local carcinoma:* There was no evidence of extension of tumor beyond the limits of the organ of origin. (No hepatic tumors were included.)

Group II: *Nonhepatic metastasis:* There was evidence of spread of tumor beyond the limits of the organ of origin, but no evidence of hepatic involvement by invasion of tumor cells.

Group III: *Hepatic metastasis:* There was evidence of involvement of the liver by tumor cells, with or without other evidence of metastasis.

The *degree of illness* (clinical index) of each patient was determined by a set of criteria graded by the examining physician. Each patient received a score ranging from zero to four points on each of four groups. The *clinical index* for the patient was the total of the four scores. Independent evaluation of any case by two or more observers always resulted in a clinical index within two points. The four major criteria were as follows:

1. The food intake for the month prior to the time of initial observation. (0 = little or none, to 4 = above average.)
2. The nutritional status of the patient at the time of physical examination. (0 = cachectic, to 4 = very well nourished, with no evidence of weight loss.)
3. The patient's subjective well-being and ability to perform normal activities.
   (0 = unable to perform beyond basal level, to 4 = very active and feeling quite well.)

4. The observer's evaluation of the patient's general clinical condition, independent of the prognostic implications of carcinoma per se. (0 = imminently terminal, to 4 = excellent condition.)

On this basis a patient could score from zero to 16 points. In fact, the observed range was from three to 16 points. The individual scores were then grouped into the following ranges:

1. Very poor to poor health: score of from three to seven points.
2. Intermediate health: score of from eight to 11 points.
3. Good to excellent health: score of from 12 to 16 points.

All data were analyzed by standard statistical technics, including P for Fisher t according to a table of distribution of t,[86] linear regression correlation coefficient utilizing the r of Pearson[87] tested by P for r of Fisher,[88]

TABLE 1

Serum Cholinesterase in Various Clinical Situations*

Category	No. Cases	Mean Serum CHE†	% < 150 U.	% > 305 U.
Fasting, normal	51	204	0	0
Postprandial, normal	64	220	0	0
Benign: out-patient‡	102	205	5	6
Benign: in-patient‡	89	178	33	2
Carcinoma patients	208	124	70	1

All mean values were significantly different from the fasting normal group except that for Benign Out-Patients.

All mean values were significantly different from the carcinoma group.

* All values were obtained on fasting subjects except those for postprandial normals.

† Units of activity per cubic centimeter.

‡ Non-neoplastic, nonhepatic, nonhypertensive.

crude correlations in percentage values by squaring the individual r values and multiple correlations based on r values.[89] In all cases of tests for significance, a 5% confidence limit was employed ($P < .05$).

RESULTS

A. Serum Cholinesterase Activity in Patients with Carcinoma. Results obtained in a series of 208 patients with carcinoma were compared with those for several other groups of individuals (table 1). Inasmuch as the postprandial normal mean value was significantly higher than that for fasting normal subjects, all other values described were obtained in the fasting state. The normal adult range for serum cholinesterase activity was established as 150 to 305 units.

In a group of 102 carefully studied out-patients with no evidence of tumor, liver disease, hypertension or pregnancy, the mean cholinesterase was essentially the same as that for normal subjects. However, in 5% of the cases the values obtained were below normal, while elevated results were demonstrated in 6% of the group. A study of 89 similar patients in

TABLE 2

Origin of Carcinoma in 208 Patients

Primary Organ	No. Cases	Mean Serum CHE*	% < 150 U.
A. Breast	34	170	32.4
B. Lung	38	133	63.2
C. Miscellaneous†	38	120	71.1
D. Lower G.I.	34	119	79.4
E. Panc., EHB‡	35	103	82.9
F. Upper G.I.§	29	92	93.1

* Units per cubic centimeter.
† Uterus, 9; oral cavity, 6; prostate, 6; kidney, 4; ovary, 4; bladder, 3; skin, 3; brain, 1; fallopian tube, 1; thyroid, 1.
‡ Pancreas, 24; bile ducts, 7; gall-bladder, 4.
§ Esophagus, 11; stomach, 18.

the hospital demonstrated a significantly lowered mean cholinesterase activity, with one third of the cases below normal and 2% above normal.

In the 208 patients with carcinoma the mean cholinesterase activity was 124 units per cubic centimeter of serum. This value was significantly lower than that in any of the aforementioned groups. Seventy per cent of these patients with carcinoma had serum cholinesterase activity below 150 units per cubic centimeter.

Of the 208 patients studied, 41 had local carcinoma (Group I), 93 had nonhepatic metastases (Group II), and 74 had hepatic metastases (Group III). The site of origin of carcinoma in these patients is indicated in table 2. It was noted that the mean cholinesterase value for carcinoma of the breast was significantly higher than that in any other group. In addition, carcinoma of the lung had a significantly higher mean value than did either pancreatic or upper gastrointestinal tumors. Furthermore, only one third of the patients with mammary carcinoma had abnormally low enzyme values as compared to over 90% of those with upper gastrointestinal tumor.

TABLE 3

Distribution of the Groups, Indicating Degree of Spread of Carcinoma According to Site of Primary Lesion

Category	No. Cases	Group I* % of Cases	Group II† % of Cases	Group III‡ % of Cases
Total	208	20	45	35
Breast	34	18	62	20
Lung	38	24	42	34
Upper G.I.	29	24	31	45
Lower G.I.	34	24	41	35
Pancreas, biliary tract	35	20	26	54
Miscellaneous	38	11	63	26

* Local carcinoma.
† Nonhepatic metastasis.
‡ Hepatic metastasis.

The percentage of cases representing the three degrees of spread of tumor was not uniform for each primary site of carcinoma (table 3). Although some of the distributions were roughly comparable, the degree of spread of tumor, rather than the site of the primary lesion, was selected as a base for most of the subsequent analysis of data.

The mean serum cholinesterase activity of the patients with local carcinoma was significantly lower than that for fasting normal control subjects

TABLE 4

Serum Cholinesterase Activity in Carcinoma: Effect of Degree of Spread of Tumor

Group*	No. Cases	Mean Serum CHE†	% < 150 Units
Benign out-patients	102	205	5
Benign in-patients‡	89	178	33
I	41	157	56
II	93	136	63
III	74	92	85

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† In units per cubic centimeter.
‡ Non-neoplastic, nonhypertensive, nonhepatic disease.

and out-patients with benign disease, but it was not significantly less than that for in-patients with benign disease. Patients with nonhepatic metastatic disease had a mean cholinesterase that was significantly lower than that in patients with local carcinoma, or in the benign in-patient group. Those with hepatic metastases had a mean value significantly lower than that in patients with nonhepatic metastasis. The incidence of abnormally low values rose from 56% to 85% as the degree of spread of cancer increased, which may

TABLE 5

Clinical Index of 175 Carcinoma Patients According to Degree of Spread of Tumor

Group*	No. Cases	Mean Clin. Index
I	39	10.4
II	86	9.4
III	50	7.9
Total	175	9.2

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.

be compared with the value of 5% for benign out-patients and 33% for benign in-patients (table 4).

Of the 175 patients with carcinoma who were assigned a clinical index rating, 39 were in the poor (three to seven) group, 86 in the intermediate (eight to 11) group, and 50 in the good-to-excellent (12 to 16) group. Patients with nonhepatic metastases had a mean value one unit lower than that of those with local cancer, while those with hepatic metastases demonstrated a mean clinical index two and one-half units below that of the local

group, and one and one-half units below that of the nonhepatic metastasis group (table 5).

When the sites of origin of tumors were arranged according to descending value for mean clinical index, their order of mean serum cholinesterase activity did not necessarily correspond (table 6). The distribution of the various degrees of illness within each group based on the degree of spread of the carcinoma indicated the possibility of some valid comparison of the

TABLE 6

Clinical Index in Carcinoma According to Site of Primary Lesion

Site of Origin	No. Cases	Mean Clin. Index*	Rank†	Mean Serum CHE	Rank†
Breast	33	10.6	1	170	1
Lower G.I.	31	9.6	2	121	3
Miscellaneous	35	9.3	3	119	4
Lung	29	8.8	4	138	2
Upper G.I.	21	8.7	5	94	6
Panc., EHB	26	7.8	6	107	5

* 3–7 = very poor to poor; 8–11 = intermediate; 12–16 = good to excellent.
† Mean values arranged from highest value (1) to lowest value (6).

interaction of these two variables with serum cholinesterase activity (table 7). It was interesting to note that quite ill patients were found in the local group and relatively healthy people in the metastatic groups.

Mean cholinesterase activity fell from 190 units for the 12 to 16 group to 166 and 162 for the lower groups in 89 patients with benign disease, and similarly fell from 169 to 122 to 96 units in the 175-patient cancer group.

TABLE 7

Degree of Illness Within Degree of Spread Groups (175 Patients): Clinical Index*

Degree of Spread†	No. Cases	3–7 % of Cases	8–11 % of Cases	12–16 % of Cases
I	39	13	44	43
II	86	22	49	29
III	50	34	58	8

* 3–7 = very poor to poor; 8–11 = intermediate; 12–16 = good to excellent.
† I = local; II = nonhepatic metastasis; III = hepatic metastasis.

However, for a given degree of sickness, the cancer patients had a lower mean cholinesterase value than did those with benign disease (table 8).

Combination of the two variables, the degree of spread of cancer and the clinical index of the patient, indicated that within each of the three groups based on the degree of spread, serum cholinesterase activity fell as the patient groups were "sicker" (table 9: horizontal lines). However, it also demonstrated that, for any given degree of sickness (clinical index), cholinesterase fell as cancer spread (table 9: vertical lines).

B. Serum Albumin in Patients with Carcinoma (Table 10). The mean serum albumin of 192 patients with carcinoma was 3.6 gm. per 100 c.c. The mean values fell significantly—from 3.9 gm. for local carcinoma, to 3.3 gm. for hepatic metastasis, with a range from 1.9 gm. to 5.1 gm. The percentage

TABLE 8

Effect of Degree of Illness (Clinical Index) on Serum Cholinesterase in Benign and Malignant Disease

Category	Clinical Index*					
	3–7		8–11		12–16	
	No.	Mean	No.	Mean	No.	Mean
Normal subjects	0	—	0	—	51	204
Benign disease†	7	162	30	166	52	190
Carcinoma	41	96	88	122	46	169

* 3–7 = very poor to poor; 8–11 = intermediate; 12–16 = good to excellent.
† In-patients with non-neoplastic, nonhepatic, nonhypertensive disease.

of values below 3.8 gm. rose from 43% for local disease to 85% for hepatic metastasis.

The correlation between cholinesterase and albumin for the entire group was 38%, with the best correlation in the local tumor patients. Group II and Group III patients had roughly the same correlation. This compared

TABLE 9

The Effect of Degree of Spread of Tumor and the Degree of Sickness (Clinical Index) on the Serum Cholinesterase Activity of Cancer Patients

Degree of Spread†	Total		Clinical Index Group*					
			3–7		8–11		12–16	
	No.	Mean	No.	Mean	No.	Mean	No.	Mean
I	41	157	5	119	17	142	17	184
II	93	136	19	115	42	130	25	165
III	74	92	17	68	29	99	4	123
		Total	41	96	88	122	46	168

* 3–7 = very poor to poor; 8–11 = intermediate; 12–16 = good to excellent.
† I = local; II = nonhepatic metastasis; III = hepatic metastasis.

with correlations between these two parameters of 50% in 131 patients with liver disease of non-neoplastic nature and 42% in 33 pregnant women (table 11).

C. Serum Globulin in Patients with Carcinoma (Table 12). There was no significant difference in mean levels of serum globulin as the degree of spread of carcinoma increased in a series of 192 patients. The mean value

TABLE 10

Serum Albumin of 192 Carcinoma Patients, Showing Correlation with Serum Cholinesterase

Group*	No. Cases	Mean Serum Alb.†	% < 3.8 gm. %	Range	% Correlation with CHE
I	37	3.9	43	2.6–5.1	49
II	89	3.6	57	2.3–5.1	29
III	66	3.3	85	1.9–5.1	28
Total	192	3.6	64	1.9–5.1	38

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† Grams/100 c.c.

for the entire group was 3.0 gm./100 c.c. Of interest was the observation that one fourth of 67 patients with hepatic metastases had serum globulin levels over 3.5 gm. No correlation was found between serum globulin levels and serum cholinesterase activity.

D. Serum Total Cholesterol in Patients with Carcinoma (*Table 13*). There was no statistically significant difference in mean total serum choles-

TABLE 11

Correlation between Serum Albumin and Cholinesterase

Group	No. Cases	% Correlation
Carcinoma	192	38
Liver disease*	131	50
Pregnancy	33	42

* Non-neoplastic.

terol levels as the degree of spread of carcinoma increased in a series of 192 patients, despite the apparent tendency for lower values in the metastatic groups. The mean value for all cases was 250 mg.%. About one fifth of all patients in each group had values in excess of 300 mg.%. No significant correlation was noted between serum total cholesterol levels and serum cholinesterase activity.

TABLE 12

Serum Globulin of 192 Carcinoma Patients, Showing Correlation with Serum Cholinesterase

Group*	No. Cases	Mean Serum Glob.†	% < 2.0 gm. %	% > 3.5 gm. %	Range	% Correlation with CHE
I	37	3.0	3	8	1.8–5.3	1
II	88	2.9	4	10	1.8–4.5	0
III	67	3.1	9	24	1.6–4.7	3
Total	192	3.0	6	15	1.6–5.3	0

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† Grams/100 c.c.

TABLE 13

Serum Total Cholesterol of 192 Carcinoma Patients, Showing Correlation with Serum Cholinesterase

Group*	No. Cases	Mean Serum Chol.†	% < 150 mg. %	% > 300 mg. %	Range	% Correlation with CHE
I	41	268	2	22	109–690	9
II	86	251	2	19	117–676	5
III	65	238	9	20	111–732	1
Total	192	250	5	20	109–732	5

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† Total cholesterol in milligrams per cent.

E. Serum Cholesterol Esterification in Patients with Carcinoma (*Table 14*). There was no significant difference in serum cholesterol esters (expressed as a percentage of the total cholesterol) as the degree of spread of carcinoma increased in a series of 180 patients. The mean value for the entire group was 62%. The percentage of values below 65% rose from about one third of cases in the local and nonhepatic metastatic group to about

TABLE 14

Serum Cholesterol Esters of 180 Carcinoma Patients, Showing Correlation with Serum Cholinesterase

Group*	No. Cases	Mean Chol. Esters†	% < 65%	Range	% Correlation with CHE
I	39	61	33	11–74	1
II	81	64	28	6–75	6
III	60	59	52	7–75	17
Total	180	62	38	6–75	7

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† As percentage of total cholesterol.

one-half of those with hepatic metastases. However, the presence of extrahepatic biliary tract or pancreatic neoplasm increased the incidence of depression of cholesterol esters from 24% to 82% (table 22).

There was a weak correlation between serum cholinesterase activity and serum cholesterol esters in the hepatic metastatic group, but none in the other two groups or in the 180 patients taken as a whole. There was a similar

TABLE 15

Correlation between Serum Cholesterol Esters and Cholinesterase

Group	No. Cases	% Correlation
Carcinoma	180	7
Carcinoma: hepatic metastasis	60	17
Liver disease*	118	19
Pregnancy	32	4

* Non-neoplastic.

weak correlation between cholesterol esters and cholinesterase in patients with hepatic disease (table 15).

F. Serum Alkaline Phosphatase in Patients with Carcinoma (Table 16). The mean serum alkaline phosphatase activity was more significantly elevated in patients with hepatic metastases than in those without. The mean value for 204 patients with carcinoma was 9.4 Bodansky units. If extra-

TABLE 16

Serum Alkaline Phosphatase in 204 Patients with Carcinoma, Showing Correlation with Serum Cholinesterase Activity

Group*	No. Cases	Mean Serum Alk. Phos.†	% > 4.9 Units	Range	% Correlation with CHE
I	40	6.3	38	1.6–38.7	0
II	93	7.4	37	1.6–73.4	2
III	71	13.8	78	1.5–49.6	3
Total	204	9.4	51	1.5–73.4	6

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† Bodansky units per cubic centimeter.

hepatic tumors of the biliary tract and pancreas were excluded, the mean was 7.7 Bodansky units for 170 patients. The incidence of abnormal values rose from a little more than one third of cases for local tumor to 78% for the hepatic metastatic group. Also, the presence of neoplasm of the extrahepatic biliary tract and pancreas increased the incidence of elevation of alkaline phosphatase over 4.9 Bodansky units from 38% to 96% of cases

TABLE 17

Serum Total Bilirubin in 203 Patients with Carcinoma, Showing Correlation with Serum Cholinesterase Activity

Group*	No. Cases	Mean Serum Tot. Bil.†	% > 1.0 mg. %	Range	% Correlation with CHE
I	40	2.9	48	0.3–18.4	0
II	90	2.6	24	0.2–29.6	3
III	73	4.1	44	0.2–36.4	3
Total	203	3.2	36	0.2–36.4	3

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† In milligrams per cent.

(table 22). There was no significant correlation between serum alkaline phosphatase and cholinesterase activity.

G. Serum Total Bilirubin in Patients with Carcinoma (Table 17). There was no significant difference in mean total bilirubin levels as the degree of spread of carcinoma increased in a series of 203 patients. The mean value for the entire group was 3.2 mg.%. About one third of all cases were elevated above 1.0 mg.%. However, the incidence of abnormal values in the group with extrahepatic biliary tract and pancreatic tumors was 82%,

TABLE 18

Serum Thymol Turbidity in 110 Patients with Carcinoma, Showing Correlation with Serum Cholinesterase Activity

Group*	No. Cases	Mean Thy. Turb.†	% > 3.9 Units	% Correlation with CHE
I	23	2.4	22	1
II	48	3.1	21	0
III	39	2.7	21	0
Total	110	2.8	21	0

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† In units per cubic centimeter.

as compared to 22% for all other cases (table 22). There was no significant correlation between serum total bilirubin and cholinesterase in these patients.

H. Serum Thymol Turbidity in Patients with Carcinoma (Table 18). No significant difference in serum thymol turbidity was noted as the degree of spread of carcinoma increased in a series of 110 patients. The mean value for the entire group was 2.8 units. About one fifth of the values were ele-

TABLE 19

Hematocrit of 201 Patients with Carcinoma, Showing Correlation with Serum Cholinesterase Activity

Group*	No. Cases	Mean Hematocrit	% < 36%	Range	% Correlation with CHE
I	38	41.9	11	30–51	9
II	91	40.4	23	23–59	6
III	72	39.3	21	27–57	2
Total	201	40.3	20	23–59	7

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.

vated above 3.9 units in all groups. There was no correlation between serum thymol turbidity and cholinesterase in these patients.

I. Hematocrit in Patients with Carcinoma (Table 19). The mean hematocrit of 201 carcinoma patients was 40.3%. Cases with hepatic metastases had a mean value significantly lower than that in patients with local disease. About one fifth of all patients had values below 36%. There was no significant correlation between hematocrit and serum cholinesterase activity in carcinoma patients or those with liver disease or pregnancy (table 20).

TABLE 20

Correlation of Hematocrit with Serum Cholinesterase Activity

Group	No. Cases	% Correlation with CHE
Carcinoma	132	7
Liver disease*	152	5
Pregnancy	231	5

* Non-neoplastic.

J. Erythrocyte Sedimentation Rate in Patients with Carcinoma (Table 21). There was no significant difference in mean sedimentation rate as the degree of spread of cancer increased in a series of 136 patients. The mean value for the entire group was 64 mm. per hour. About 70% of all cases were elevated beyond 39 mm. per hour. A weak but significant correlation

TABLE 21

Erythrocyte Sedimentation Rate in 136 Carcinoma Patients, Showing Correlation with Serum Cholinesterase Activity

Group*	Cases	Mean ESR†	% > 39 mm./hr.	Range	% Correlation with CHE
I	23	61	74	13–126	17
II	56	58	64	1–115	0
III	57	71	77	2–128	0
Total	136	64	71	1–128	1

* I = local; II = nonhepatic metastasis; III = hepatic metastasis.
† Millimeters/hour.

between sedimentation rate and serum cholinesterase activity was noted in local carcinoma, but not in metastatic disease or in the entire series of patients studied.

K. Incidence of Five Abnormal Parameters in Carcinoma Patients. In a series of 162 carcinoma patients (33 local, 78 nonhepatic metastatic, and 51 hepatic metastatic), serum cholinesterase, albumin, cholesterol esters,

TABLE 22

Incidence of Abnormal Tests in 162 Carcinoma Patients*†

Group	No. Cases	Serum CHE‡	Serum Albumin§	Serum Chol. Esters‖	Serum Alk. Phos.¶	Serum Bil.**
A. All except B	135	67	66	24	38	22
B. EHBT, pancreas††	27	78	56	82	96	82
C. Total	162	69	64	33	48	32

* Patients selected had all five tests performed concurrently.
† Expressed as percentage of total number of cases.
‡ % < 150 units per cubic centimeter.
§ % < 3.8 gm. per 100 c.c.
‖ % < 65% of total cholesterol.
¶ % > 4.9 Bodansky units per cubic centimeter.
** % > 1.0 mg. %.
†† Extrahepatic biliary tract and pancreatic tumors.

alkaline phosphatase and total bilirubin were determined concurrently. It was noted that two or fewer tests were abnormal in half of the cases, one or none in almost one third, and none in 9%. All five were abnormal in only 14% of cases. Cholinesterase was normal in the presence of one or more other abnormalities in 35 cases (24%).

L. Correlation of Individual Parameters with Serum Cholinesterase (Table 23). Of the nine laboratory tests measured, only one showed sta-

tistically significant correlation with serum cholinesterase activity, namely, serum albumin. This was of the order of a 38% relationship. In addition, there was a weak but significant correlation between the degree of illness of the patients (clinical index) and serum cholinesterase activity (21%).

TABLE 23

Relation of Various Parameters to Serum Cholinesterase Activity in Patients with Carcinoma

Test	No. Cases	% Correlation with CHE*
Albumin	192	38†
Cholesterol esters	180	7
Alkaline phosphatase	204	6
Total cholesterol	192	5
Total bilirubin	203	3
Globulin	192	0
Thymol turbidity	110	0
Hematocrit	201	7
Sedimentation rate	136	1
Clinical index	175	21†
Alb., clin. index, CHE	165	48†‡

* Pearson r squared.
† Statistically significant.
‡ Multiple correlation coefficient.

The only multiple correlation of statistical significance was that between serum albumin, clinical index and serum cholinesterase activity. This indicated a 48% relationship of the three parameters.

M. Benign vs. Malignant Extra-Hepatic Obstruction (*Table 24*). When an arbitrary dividing point of 160 units of serum cholinesterase activity was used, 83% of 60 patients with clinical evidence of obstructive jaundice had

TABLE 24

Serum Cholinesterase Activity in Benign and Malignant Obstructive Jaundice

	No. Cases	No. >160 Units	% >160 Units	No. 160 Units or Less	% 160 Units or Less
Malignant	34	4	12	30	88
Benign	26	20	77	6	23
Total	60	24	40	36	60

Over-all accuracy: 83%.

surgical findings consistent with a preoperative prediction based on the enzyme level. Of 34 patients with proved neoplastic disease causing the obstruction, only four had serum cholinesterase values over 160 units, whereas six of 26 patients with a benign cause of obstruction had values 160 units or lower. In addition, only one benign case had a value below 140 units. Of the 11 cases that fell in the range from 140 to 160 units, six had malignant disease and five had benign disease.

Discussion

The analysis of the depression of serum cholinesterase activity in patients with carcinoma required evaluation of the factors which influence this enzyme in both non-neoplastic and neoplastic disease, the possible explanations of its depression, the implications arising from these explanations, and the practical clinical significance of its determination in the cancer subject.

Although the function of serum cholinesterase remains enigmatic, it is known that it is produced by the liver, possibly in a crude association with albumin. Consequently, progressive increments in hepatocellular damage produce progressive decline in enzyme production, which is reflected by lowered serum enzyme activity. Thus, it is useful in the evaluation of the amount of involvement of the hepatic parenchyma by cirrhosis or inflammatory processes and in the evaluation of the day-to-day dynamic changes of the acute viral hepatitides.

Serum cholinesterase activity has also been found to be low in a number of generalized pathologic conditions characterized by moderately severe to severe illness, with or without evidence of general nutritional deficiency. In these patients, albumin levels are often below normal, suggesting a relationship between albumin and cholinesterase synthesis. However, it has also been found to be significantly lowered in women during normal pregnancy, in whom statistically only a partial correlation with albumin levels has been demonstrated, and in hepatic disease, where, again, only an incomplete association between albumin and cholinesterase has been noted.

Abnormally elevated serum cholinesterase levels are seen in nephrosis (where increased albumin and cholinesterase synthesis, combined with significant loss of albumin but not cholinesterase in the urine, may explain the phenomenon), essential hypertension and, perhaps, severe anxiety states.

In addition, a number of drugs and poisons may temporarily inhibit serum cholinesterase activity until the liver generates enough enzyme to raise serum levels to normal, or until the effect ends by metabolism of the agent.

Of these many variables, all but a few could be excluded in the series of 208 carcinoma patients studied. Patients who were pregnant or who had associated non-neoplastic liver disease, severe infection, collagen disease, psychoses, essential hypertension or nephrosis were readily detectable and were omitted from the series. All observations were taken when the patients were not under the influence of agents exerting anticholinesterase activity. Severe anxiety was present in many instances. However, this factor tends to raise rather than to lower cholinesterase, and would therefore bias results in a direction opposite to that of the major findings.

Hepatic involvement by tumor invasion, with a resultant decrease in the number of functional cells available for the manufacture of cholinesterase, was not excluded but, rather, was placed in a separate category of tumor patients. The degree of illness was also classified in three general groups

which could be compared with similar groups of patients with non-neoplastic disease. Thus it was possible to analyze the role of the liver (including its capacity to synthesize albumin) and the degree of illness, as well as the part played by the tumor itself in the depression of serum cholinesterase activity seen in these patients.

There was no doubt that serum cholinesterase activity was significantly depressed in this series. The mean value was 80 units less than that for normal adults or out-patients with non-neoplastic disease, and 54 units lower than that for in-patients with benign disease.

The depression of enzyme activity was not considered to be primarily related to hepatic dysfunction for the following reasons: (1) lowered values were noted in many patients with no morphologic hepatic involvement by tumor cell invasion or the degenerative changes of extrahepatic obstruction; (2) many patients with low serum cholinesterase activity exhibited no other abnormality of hepatic function by chemical tests; (3) there was no linear correlation between serum cholinesterase activity and several manifestations of liver function, including cholesterol esterification, alkaline phosphatase activity, total bilirubin levels, globulin levels, thymol turbidity and total cholesterol levels.

A statistically significant relationship was found between serum cholinesterase activity and serum albumin levels in these patients. However, it was only of the order of 38%, indicating that other factors *must* be related to the enzyme defect noted. Patients in the more widespread tumor group showed an even weaker relationship between the enzyme and albumin. The correlation observed in patients with carcinoma was not dissimilar to that seen in patients with liver disease or pregnancy. This, then, demonstrated that the fall in serum cholinesterase activity in patients with carcinoma can no longer be dismissed as merely a reflection of decreased protein synthesis in the tumor state. The older theory, which said that the latter was the case, was based in part on a comparison of mean values rather than on correlation statistics, which are essential in a proper evaluation of any set of two or more variables.

With regard to the degree of sickness (clinical index) of these patients, there was a significant but small relationship between serum cholinesterase activity and the general well-being of the individuals studied. However, in any group of equally sick patients, those with carcinoma had significantly lower serum cholinesterase activity than did those with non-neoplastic disease. In addition, there was some overlap between clinical index and albumin levels, so that the general intercorrelation of degree of illness, albumin and cholinesterase was of only a 48% order. In other words, some factor or factors other than how sick the patients were, how poorly their livers synthesized albumin, and how their liver cells functioned in general, played a major role in the depression of enzyme activity in these carcinoma patients.

It is here suggested that the tumor itself was the missing contributory factor in the depression of serum cholinesterase noted in patients with carcinoma. In addition to the processes of exclusion of other factors heretofore cited, certain positive information supporting this hypothesis has also been elicited.

First, there was a steady decline in mean enzyme values in the groups of patients as the spread of carcinoma increased. The fall from a mean of 157 units for patients with local carcinoma to 136 units for nonhepatic metastases is statistically significant, as is the additional fall to 92 units seen in patients with metastatic tumor in the liver. The latter figure is less meaningful, since in this group the liver played some role in the depression of cholinesterase resulting from a decreased manufacture of the enzyme.

A second observation is that, for any given degree of illness, values for patients with carcinoma were lower than were those for equally ill patients with non-neoplastic diseases. Finally, for any degree of illness the mean cholinesterase values were lower as the extent of cancer increased. In other words, although two groups of patients might have been in a roughly equivalent state of health, those showing metastatic cancer showed a lower mean serum cholinesterase activity than did those with local tumor.

Of lesser importance, but suggestive of the role of the tumor in effecting the fall of cholinesterase noted, was the observation that certain tumors (breast and lung) appeared to exhibit less effect on the enzyme levels than did other tumors (pancreatic or upper gastrointestinal). Earlier observations had indicated a still weaker influence for lymphomas or leukemia as compared to carcinoma.

If one accepts the proposition that a major relationship exists between tumor tissue—specifically, carcinomatous tissue—and serum cholinesterase activity, certain possibilities become apparent. The first is that the tumor tissue may incorporate serum cholinesterase in its metabolic activity. However, since no known physiologic function has been found for this enzyme, this remains purely speculative. The second is the possibility that the tumor may inhibit the manufacture of the enzyme by normal liver cells. This is probably partially correct, as the correlation studies with albumin indicated. Another possibility is that the tumor produces or activates an inhibitor of serum cholinesterase. The fact that such a substance has not previously been demonstrated by simple in vitro mixing or dialyzing technics does not exclude this possibility. In vitro biochemical experiments and in vivo studies of animal tumors may clarify this matter in the near future.

Should the tumor be found to exert an anticholinesterase effect, one must then determine whether the progressive decline in enzyme activity noted as patient groups exhibited increased amounts of tumor was simply a direct relationship of the tumor mass to the amount of antienzyme produced. More important, the enzyme-inhibiting function of carcinomatous tissue may be related to its transition from the dependent to the autonomous state.

If so, such information would be a significant forward step in the further understanding of the physiology of the tumor tissue itself.

The question of the practical clinical significance of the serum cholinesterase test in the evaluation of patients with carcinoma is raised by a study of patients with clinical obstructive jaundice in whom the etiology was determined by surgical exploration. In a series of 60 such patients, 83% accuracy in the prediction of a benign or neoplastic cause of the obstruction was obtained by drawing an arbitrary line at a serum cholinesterase activity of 160 units per cubic centimeter. In addition, 70% of the 208 patients with carcinoma studied had cholinesterase values below normal. Of those with local carcinoma, 56% of the results were low, 63% of patients with nonhepatic metastatic tumor had low values, and 85% of those with hepatic metastases were below normal.

It is our opinion that when an adult patient not exposed to agents with anticholinesterase activity, not pregnant and not suffering from liver disease, severe infection or collagen disease has a serum cholinesterase activity less than 150 units, the diagnosis of cancer is a strong possibility. Furthermore, given a patient with the preceding criteria who has had a histologically confirmed carcinoma, a decline in enzyme activity at any future time is highly suggestive of spread of the disease. The possible use of this test in the evaluation of the results of cancer therapy should also receive attention in the near future.

In conclusion, it should be noted that such enzymes as the transaminases, dehydrogenases, aldolases and certain peptidases appear in elevated amounts in serum as a coincidental result of the injury of the normal or pathologic cells which contain them. Serum cholinesterase, on the contrary, unlike the aforementioned "fortuitous" enzymes, is depressed in liver disease because of a decreased capacity to manufacture it. Its depression in carcinoma is due at least in part to the tumor itself, probably acting through an enzyme-inhibitor effect inherent in carcinomatous tissue.

Summary

A significant depression of serum cholinesterase activity was noted in patients with carcinoma. This was more marked in those groups with metastatic than with only local disease. It did not depend primarily upon hepatic parenchymal involvement due to tumor cell invasion or prolonged extrahepatic biliary obstruction. This was confirmed by clinical, radiologic and pathologic studies, in addition to analysis of a series of liver function tests.

Depressed protein synthesis by the liver, as reflected by serum albumin levels, did not in itself explain the enzyme phenomenon noted, although related to it. The correlation between cholinesterase activity and serum albumin levels, and the intercorrelation between these two parameters and the degree of illness of the individual patients indicated that the general

effect of such factors as nutritional deficiency and poor general physical condition had only a partial influence on the depression of the enzyme.

It is thought that carcinomatous tissue per se was a major factor in the lowering of serum cholinesterase activity. In support of this statement were the observations that patients with carcinoma had lower enzyme values than did equally ill patients with benign diseases, and that patients with metastatic carcinoma had lower enzyme values than did equally ill patients with local tumor. The primary site of origin of the tumor also exerted some influence on the enzyme activity. It is postulated that carcinomatous tissue produces or activates an inhibitor to serum cholinesterase.

Measurement of serum cholinesterase activity is a useful adjunct to other clinical methods of detecting the presence of carcinoma and of determining its degree of spread in the individual patient. It has potential usefulness in assaying the effect of therapy. Finally, it is 83% accurate in predicting a benign or malignant lesion as the cause of obstructive jaundice.

Summario in Interlingua

Cholinesterase seral (= pseudocholinesterase), fabricate per le hepate e clarmente differente in su comportamento biochimic ab acetylcholinesterase neuromuscular, es deprimite in un numero de prestemente detegibile conditiones clinic. Previe reportos ha signalate que le activitate de cholinesterase seral es deprimite in patientes con carcinoma. Isto esseva confirmate in un serie de 208 patientes con cancere e nulle altere condition que cognoscitemente reduce le nivello seral de iste enzyma.

Esseva effectuate un evalutation del factores que exerce un influentia super iste enzyma in situationes tanto non-neoplastic como etiam neoplastic, del explicationes possibile de iste depression, del consequentias inherente in iste explicationes, e del signification practic del determination de illo ab le puncto de vista clinic in le patiente afficite de cancere.

Un grado significative de depression del activitate de cholinesterase seral esseva notate in patientes con carcinoma. Isto esseva plus marcate in patientes con metastases que in patientes con morbo local. Illo non dependeva primarimente de un invasion del parenchyma hepatic per cellulas tumoral o de un prolongate obstruction biliari extrahepatic. Isto esseva confirmate per studios clinic, radiologic, e pathologic, a parte le analyse de un serie de tests del function hepatic.

Le depression del synthese de proteina in le hepate, reflectite in le nivellos seral de albumina, non sufficeva per se a explicar le mentionate phenomeno enzymatic, ben que un relation inter le duo debe esser supponite. Studios del correlation inter le activitate de cholinesterase e le nivellos seral de albumina e inter iste duo factores e le grado de morbiditate del patiente individual indicava que deficientias nutritional, le mal condition physic general del patiente, e simile constatationes esseva solmente in parte le causa del depression enzymatic.

Es opinate que le presentia de tissu carcinomatose per se esseva un major factor in le reduction del activitate de cholinesterase seral. Iste conception esseva supportate per le facto que patientes con carcinoma habeva plus basse valores pro le enzyma que equalmente malade patientes con morbos benigne e que patientes con carcinoma metastatic habeva plus basse valores pro le enzyma que equalmente malade patientes con tumores local. Le sito de origine del tumor primari etiam exerceva un influentia super le activitate del enzyma. Es postulate que tissu carcinomatose produce un inhibitor de cholinesterase seral o effectua le activation de un tal.

Le mesuration del activitate de cholinesterase seral es un adjuncto utile al jam disponibile methodos de deteger le presentia de carcinoma e de determinar le grado de su diffusion in le patiente individual. Illo es potentialmente utile in evalutar le effectos del therapia. E finalmente, illo es satis accurate como medio pro differentiar inter le benignitate e malignitate de un lesion que causa jalnessa obstructive.

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PECULIAR FAMILIAL AND MALIGNANT PHEOCHROMOCYTOMAS OF THE ORGANS OF ZUCKERKANDL *

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Introduction

Pheochromocytomas of the organs of Zuckerkandl are rare tumors that are primarily benign. We are aware of only three malignant lesions involving these organs previously reported in the literature.[8]

The purpose of this paper is to discuss the familial and malignant aspects of pheochromocytomas, especially of the organs of Zuckerkandl, and to present three case reports.[1, 2, 4, 9, 12, 18]

Presentation

Pheochromocytomas may arise either from the medullary tissues of the adrenals or from chromaffin tissue located elsewhere in the body. The majority of chromaffin tumors occur in the adrenal gland. About 10% of pheochromocytomas occur in extra-adrenal chromaffin tissue, such as the paraganglia of the sympathetic nervous system. Rarely, the organs of Zuckerkandl are involved in this type of tumor. The organs of Zuckerkandl are composed of paraganglionic bodies made up of chromaffin cells located adjacent to the aorta near the origin of the inferior mesenteric arteries. The organs of Zuckerkandl are found easily in infancy but usually disappear by the age of two years. When they occasionally persist to adult life, they have the potential for neoplastic development.

Chromaffin tissue tumors have been referred to as chromaffin cell tumors, chromaffinomas, paragangliomas and pheochromocytomas. We intend to use the term "pheochromocytoma" for the entire group of chromaffin cell tumors.[1]

Pheochromocytomas are usually benign but are malignant in approximately 5% to 10% of the cases.[16] Previous reports have presented familial pheochromocytomas associated with neurofibromas.[17] It has been estimated that neurofibromatosis is associated with 5% of the cases of pheochromocytoma.[9] A familial history with regard to pheochromocytoma has also

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been reported to be more common when there is an associated neurofibromatosis.[1, 6] A peculiar familial relationship possibly occurs in pheochromocytomas of the organs of Zuckerkandl, and, when present in the small percentage of cases, does not appear to be associated with a neurocutaneous syndrome.[1, 6]

Pheochromocytomas, whether of the adrenal or extra-adrenal tissue, are made up of cells identical to those of the adrenal medulla.[19] Histologically, these cells are arranged in nests and clusters enclosed in a highly vascularized fibrous stroma.[16] Lipochrome and brown pigment are present in the chromate-fixed tissue within the cell cytoplasm. Considerable variation in the differentiation of the cells may be evident.[16] When anaplastic, these tumors may metastasize to the liver, lungs, bone, regional lymph nodes and other organs.[20]

The benign tumors are well encapsulated and show no tendency to invade surrounding tissue but do compress adjacent structures. Compression produced by the enlarging tumor may be one of the factors in producing pain. These tumors are also highly vascular, and the cells are separated by numerous capillary channels. Multiple infarcts with necrosis contribute to the abdominal symptoms often produced by these tumors.[16, 19, 20]

The symptomatology of the tumors depends upon the pharmacologic activity, location and size. The pharmacologic activity of norepinephrine and epinephrine produces varying degrees of paroxysmal or persistent hypertension, cardiac palpitation, occipital headaches, vasomotor phenomena, and numerous gastrointestinal symptoms. The pheochromocytoma may selectively produce excessive amounts of epinephrine with hyperperistalsis, palpitation, nervousness and diabetes mellitus as predominant symptoms.[9] The abdominal symptoms need further emphasis, for they may be the major presenting complaints, and they have been evident in approximately 15% of the cases.[6, 18, 19] Acute abdominal pain associated with hypertension should alert the physician to the possible presence of a pheochromocytoma.[9] Infarction of the pheochromocytoma often produces acute and severe abdominal pain. Chronic abdominal symptoms may result from compression of surrounding structures by the enlarging tumor. This pain may radiate to the epigastric area or remain in the location of the tumor. An abdominal mass may be palpated in 15% of the cases, and it can represent either the tumor itself, or a kidney or liver displaced by the tumor.[19] When a palpable abdominal mass is manipulated, or indirectly stimulated by increasing intra-abdominal pressure, a hypertensive episode may be precipitated.[9]

The pharmacologic tests, such as the administration of histamine, dioxobenzane, Dibenamine and phentolamine (Regitine), are important but have been known to yield false-negative and false-positive results. Patients with pheochromocytomas often excrete excessive amounts of norepinephrine and epinephrine in their urine.[4, 7] Occasionally, the excretion of these catecholamines is only intermittently elevated, and this is often the case when the

hypertension is paroxysmal in type. Stimulation of the tumor by histamine injection or general anesthesia may raise the catecholamines excretion of the urine to diagnostic levels.[4] The determination of catecholamines in the urine is a test which possesses a high specificity for determining the presence of pheochromocytoma.[10]

Case Reports

Case 1. A 31 year old white man, admitted to Penrose Cancer Hospital in February, 1956, had noted emotional tension, nervousness, excessive perspiration, pain in the right lower quadrant and palpitation since 1950. Sharp shooting pains in the midthoracic spine and weakness had been present since 1955, at which time he had sought medical attention. Pain in the right lower quadrant had been moderately severe at times, persistent in type and increasing in severity. In March, 1955, paresthesia and incoördination of movements developed in both lower extremities. X-ray studies of the spine revealed that the seventh thoracic vertebra and pedicle were destroyed by an osteolytic process. A laminectomy revealed the presence of a destructive lesion in the laminae of the sixth and seventh thoracic vertebrae and an epidural mass occupying the same level. This was partially resected to decompress the spinal cord. On histologic examination this was reported to be a metastatic epithelial tumor. Postoperatively, the patient developed new osteolytic lesions of the fifth and sixth cervical vertebrae and the first and second lumbar vertebrae. The pelvic bones and both parietal bones of the skull appeared to be involved in an osteolytic process. Physical examination on admission, in February, 1956, revealed a well developed, well nourished white male. His gait was unsteady, his legs widely spaced, and he showed poor equilibrium and coördination. His pulse rate was 128; the blood pressure, 195/100 mm. of Hg. A grade II systolic murmur, blowing in type, was heard at the apex. A moderate amount of tenderness could be elicited along the right pubic bone and over the fifth, sixth and seventh thoracic vertebrae posteriorly. The patient was given radiotherapy over the affected areas. The sections of the epidural mass were reviewed and it was considered to represent a peculiar metastatic vascular tumor or a malignant pheochromocytoma. A chromaffin reaction was not performed on the tissue at that time. His general condition deteriorated, and he died on June 20, 1956, six years after the onset of his first symptoms. Catecholamine studies were not made on the patient's urine. The autopsy revealed a mass at the emergence of the inferior mesenteric artery, just above the bifurcation of the aorta. It was a dark brown, rubbery, multilobulated tumor, measuring 3.0 by 2.0 by 2.0 cm. The mass was situated anteriorly and extended to the right of the aorta, and it was covered by a well defined capsule. Grossly, there was no invasion of the surrounding tissues. The cut section showed a purple-red color and a granular surface, with lobules separated by thin septa arising from the capsule. It had the appearance of an exceedingly well vascularized tumor. The right wing of the ilium, the pubic rami and the vertebral bodies of C-5, C-6, C-7 and L-2 were involved by similar hemorrhagic metastatic tumor, with destruction of the affected bones. The microscopic appearance of the tumor showed a lobular architecture separated by broad bands of vascular connective tissue. The capsule was well defined but showed islands of tumor cell infiltration, especially around the blood vessels and nerves. The tumor cells were arranged in nests, with a highly vascularized stroma containing irregular vascular channels, narrow in some areas and wide in others. Areas of hemorrhage were noted. The limits of the tumor cells were not well defined. A syncytium of cells with pale and foamy cytoplasm was seen in certain sections. The difference in the size of the cells was not remarkable. The nuclei were round or oval in shape, and dark, with condensed chromatin. Mitotic figures were scanty. Lipochrome and

brown pigment were present in the chromate-fixed tissue within the cell cytoplasm. The diagnosis was malignant pheochromocytoma.

Case 2. This 42 year old white female, sister of case 1, was seen at St. Francis Hospital in July, 1957, at which time her chief complaint was pain in the lower right abdominal quadrant. She had been seen previously by her family physician for a labile hypertension, at which time her blood pressure had ranged from 140/90 to 200/120 mm. of Hg. Because of irregular uterine bleeding, the patient had a dilatation and curettage. Histologic examination of the endometrial curettings revealed an adenocarcinoma of the uterus. During the anesthetic the blood pressure spiked to 240/140 mm. of Hg and then fell precipitously to hypotensive ranges. This was followed by a convulsive seizure. Electrocardiograms at this time revealed ST and T-wave depression of 1.0 mm. over the precordial leads, which persisted on serial tracings. It was thought that the patient had had a subendocardial infarction. She was treated with roentgen therapy for her uterine cancer, and later returned to the hospital (October 22, 1957), at which time Regitine tests were performed and were within normal limits. Her blood pressure on this occasion was recorded at 150/100 mm. of Hg. Funduscopic examination of her eyegrounds revealed a 1 plus arteriosclerotic change. A grade II mitral systolic murmur was heard, with accentuation of the mitral first sound. A diastolic murmur was heard on occasions in the mitral area. On November 22, 1957, another electrocardiogram showed a normal tracing. A general anesthetic was given and urinary catecholamines were estimated. During the general anesthesia the blood pressure again spiked to 240/140 mm. of Hg but did not again drop to hypotensive ranges. The urine catecholamines at this time revealed a level of 20 μg./100 c.c. Presacral carbon dioxide injections were performed and were within limits. On December 9, 1957, the patient was again returned to the hospital for further studies. At this time a general anesthetic was again given and, again, a rise in blood pressure was noted, to 240/120 from 150/100 mm. of Hg. The urine was again collected for study of the catecholamine, and a level of 20 μg./100 c.c. was reported. An intravenous histamine test was given, injecting 0.025 mg. of histamine base, which did not cause a rise of the blood pressure. The level of urinary catecholamines, collected following histamine stimulation, was 28 μg./100 c.c. On December 31, 1957, exploratory laparotomy was performed under general anesthesia. Regitine was given at the onset because of a rise in blood pressure to 200/120 mm. of Hg, and this controlled the hypertension satisfactorily. A tumor mass was found approximately at the site of the origin of the inferior mesenteric artery, just at the bifurcation of the aorta. Examination of the adrenal areas revealed no evidence of a tumor. The mass was removed, and the patient withstood the procedure moderately well. Grossly, the tumor measured 5.5 by 3.5 by 3.0 cm. in dimension and appeared to have a definite capsule. It was soft and yellowish gray to hemorrhagic in appearance. Microscopic examination revealed a definite capsule composed of laminated fibrous tissue. Occasional large, distended capillary channels were seen in the capsule. Delicate to large trabeculae of fibrous tissue emanated from the capsule and penetrated into the tumor, producing lobulations. These fibrous trabeculae contained large venous channels and some thick-walled arterioles. The tumor itself was composed of cords and nests of cells intimately associated with thin-walled vascular channels. Fresh focal hemorrhages were noted in the tumor, but no areas of necrosis. Some of the tumor cells displayed vague borders, but most had a definite polyhedral shape, with granular eosinophilic cytoplasm and oval or round basophilic nuclei. The nuclei for the most part showed a coarsely stippled chromatin pattern, and some displayed prominent nucleoli. In a few instances there were rather prominent yellowish green granules within the cytoplasm of the tumor cells. Lipochrome and brown pigment were present in the chromatin-fixed tissue within the cell cytoplasm. Mitotic figures were rare. Oc-

casionally, nuclei were displayed which showed lobular configuration and were very hyperchromatic. In a few areas there were compressed syncytial masses of cells displaying very acidophilic cytoplasm; which was interpreted as a pheochromocytoma. The tumor weighed 25 gm. The catecholamine content per gram of tumor weight was 2.1 mg., with an adrenalin-to-noradrenalin ratio of 0.3 : 1.8 mg. In this tumor, the catecholamine excretion in the urine for 24 hours was approximately 0.33 mg., with an estimated production by the tumor of approximately 8 mg. per 24 hours.

Case 3. This 37-year-old white male entered St. Francis Hospital on February 4, 1958, complaining of pain in the right lower quadrant, severe occipital headaches, excessive perspiration and extreme nervousness. Prior to admission the patient had been examined because of his abdominal pain and labile hypertension, with a blood pressure ranging from 160/100 to 240/140 mm. of Hg. At the time of his examination, funduscopic findings showed retinal hemorrhages and cotton-wool areas within the retinae. The blood pressure was 240/140 mm. of Hg. The left border of the heart was enlarged to the left of the midsternal line. The aortic second sound was loud and snapping, and a blowing systolic murmur was present over the third left intercostal space. There was tenderness over the cecum and descending colon, but palpation did not precipitate hypertension. Laboratory studies showed a positive Regitine test in which the blood pressure dropped from 240/140 to 150/100 mm. of Hg after 30 seconds. A similar fall was present after dioxobenzane. Renal studies showed creatinine to be 1.5 mg.% and urea nitrogen, 19.8 mg.%. A glucose tolerance test revealed a diabetic curve, and basal metabolic rate was plus 30%. The 17-ketosteroids were 7.8 mg./24 hours. The initial study of catecholamines revealed 2 μg.%. After a general anesthesia the catecholamines were 6 μg.%. Fluoroscopic examination of the chest revealed concentric hypertrophy of the left ventricle. Intravenous pyelograms were normal, as were the results of presacral carbon dioxide injections. Electrocardiographic findings were compatible with left ventricular hypertrophy. The histamine test was not done because of the persistent electrocardiographic changes. On March 22, 1958, an exploratory laparotomy was performed. A tumor mass was found adherent to the aorta and to the vena cava, just below the origin of the inferior mesenteric artery and to the right of the bifurcation of the aorta. This tumor measured 3.0 by 2.0 by 1.7 cm. There were several small nodules directly below the origin of the tumor and below the bifurcation of the aorta. After removal of the tumor the patient's blood pressure was maintained on Levophed for 28 hours, after which the postoperative course was uneventful. Grossly, the tumor appeared to be soft and pinkish gray in color. The total weight was 10.6 gm. Microscopic sections of the small nodules revealed lymph nodes in which there were lobulated portions of tumor tissue. Here, the tumor was composed of polyhedral cells with granular acidophilic cytoplasm. Lipochrome and brown pigment were present in the chromate-fixed tissue within the cell cytoplasm. The cells were arranged in small nests and in anastomosing trabeculae. Between the nests and the trabeculae of cells there were prominent vascular channels. The tumor cells actually appeared to form the walls of some of these vascular channels and had oval, round and somewhat elongated basophilic nuclei. Many of the nuclei were very hyperchromatic and had considerable lobulation and deformity. There was great pleomorphism as far as the nuclei were concerned, with giant sized nuclear forms. Only occasional mitoses were seen, and no definitely atypical mitotic figures could be identified. The principal tumor mass, anterior to the aorta, showed a definite fibrous capsule, and within the capsule there were nests of tumor cells, particularly around the blood vessels and bundles of nerve fibers. Fibrous septa penetrated into the tumor from the capsule. Because of the presence of tumor cells within lymph nodes and the histologic appearance, the tumor was considered to be an anaplastic pheochromocytoma. The total weight of the tumor was 10.6 gm., and the combined

weight of the tumor and the material removed from the periaortic region was 12.6 gm. The total catecholamines extracted from this tumor were 0.95 mg./gm. Of this, less than 0.10 mg. was identified as adrenalin, whereas noradrenalin composed approximately 0.85 mg. In this patient the approximate excretion rate was 0.17 mg./24 hours, indicating a total production of approximately 4.3 mg./24 hours. The above figures were based on the excretion rate of approximately 4% as indicated in a normal human subject, according to von Euler.

Discussion

The majority of pheochromocytomas are located in the adrenal glands, but 10% are located elsewhere in the body. The organs of Zuckerkandl rarely persist to adult life, but when this occurs, they have a potential for neoplastic change. Tumors in these organs are infrequent but are even more of a medical curiosity when they become malignant. We are aware of only three earlier reports of malignant pheochromocytomas of the organs of Zuckerkandl.[8] Our additional two malignant tumors of these organs bring the total cases to five. The previously reported cases did not appear to show physiologic activity, but both of our malignant tumors were actively secreting excesses of catecholamines.[8]

A familial occurrence of pheochromocytoma has previously been reported.[1, 6, 17] Approximately 5% of the cases of pheochromocytomas in the literature have been associated with neurofibromatosis.[19] A familial history is common when associated with neurocutaneous neoplastic diseases. However, there was no evidence of neurocutaneous disease in our two familial cases. Possibly there is a peculiar familial relationship in pheochromocytomas of the organs of Zuckerkandl with or without the concurrent neurocutaneous disorders.

In addition to the symptoms of palpitation, excessive perspiration, headaches and tachycardia, the gastrointestinal complaints seemed paramount in the history of each of our cases. Widespread metastases were evident in our first case, involving bone and spinal cord. The diagnosis was made at postmortem examination. Laboratory studies for excess of catecholamines were not performed in case 1, but the symptoms were certainly suggestive of physiologic overactivity. The second case, a sister of case 1, had paroxysmal hypertension and abdominal pain, and the urinary catecholamines were normal on initial studies. The histamine test and general anesthesia produced enough stimulation to raise the catecholamine excretion to diagnostic levels. Interestingly, the pharmacologic tests in case 2 were consistently negative, but stimulation with histamine, even though it did not cause a rise in blood pressure, did cause an increased excretion of catecholamine in the urine. In case 3, the Regitine and dioxobenzane tests were repeatedly positive. However, catecholamine excretion levels in the urine were within normal limits, even after a general anesthesia. This demonstrates the diagnostic limitations of catecholamine excretion as well as the pharmacologic tests, in the presence of an actively secreting pheochromocytoma.

Summary

A pheochromocytoma is a rare tumor that is primarily located in the adrenal gland. Rarely, the organs of Zuckerkandl are involved in this type of tumor. Three previous malignant pheochromocytomas have been reported. We have reviewed the literature and presented three additional pheochromocytomas of the organs of Zuckerkandl, two malignant and pharmacologically active, and two with familial characteristics. Diagnostic limitations of the pharmacologic tests and of catecholamine excretion were discussed.

Acknowledgment

Appreciation is expressed for the constructive suggestions of Dr. Morgan Berthrong.

Summario in Interlingua

In le majoritate del casos, pheochromocytomas es locate in le glandulas suprarenal, sed 10% de illos es locate alterubi in le corpore. Le organos de Zuckerkandl persiste rarmente usque al vita adulte, sed quando isto occurre, illos manifesta le potentialitate de alterationes neoplastic. Le formation de tumores in iste organos es infrequente e representa un curiositate medical. Secundo nostre information, il existe in le litteratura solmente tres previe reportos de maligne pheochromocytomas del organos de Zuckerkandl. Nostre reporto de duo casos additional de maligne lesiones de ille organos augmenta le total a cinque casos reportate. In le casos previemente describite, nulle activitate physiologic esseva notate, sed in ambe nostre casos de malignitate il habeva excessos del secretion de catecholaminas.

Le occurrentia familial de pheochromocytoma ha essite reportate in le passato. Approximativemente 5% del casos notate in le litteratura esseva etiam associate con neurofibromatosis. In nostre duo casos familial il non habeva un historia de neurofibromatosis. Il es possibile que il se tracta hic del phenomeno peculiar de un persistentia familial usque al etate adulte del organos de Zuckerkandl, con un augmentate predisposition al formation de pheochromocytomas sin o con disordines neurocutanee.

A parte le symptomas de palpitation, excessos de perspiration, e tachycardia, le presentia de gravamines gastrointestinal pareva esser le plus frappante characteristica del historia clinic in ambe nostre casos. Esseva notate un restringite valor de studios pharmacologic e etiam de studios del excretion de catecholamina. Le problemas incontrate es discutite.

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THE NORMAL SYSTOLIC MURMUR*†

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The terms "physiologic," "functional," "innocent" and "benign" have customarily been applied to heart murmurs which, by definition, arise in presumably normal hearts. Such designations imply a distinction between these sounds and those produced by some abnormality of the cardiovascular system (though not necessarily excluding extracardiac disease, such as anemia or hyperthyroidism). The concept of functional vs. pathologic murmurs is perhaps more clinically useful than decisive; generally the assumption is that an individual either does or does not have a murmur, and that if he does it either is or is not indicative of organic heart disease.

It has been variously estimated that from about 5 to 15% of normal subjects have functional heart murmurs which are audible on stethoscopic examination. For example, 7% of almost 3,000 students at Harvard College[1] were found to have systolic murmurs for which no organic basis was evident. This percentage increases to 25 or even 50% in children,[2] doubtless due in part to their thinner, more resilient chest walls. Ordinarily such murmurs are of comparatively low intensity, systolic in time, often inconstant, usually heard best at the base of the heart or along the left sternal border, and are notably altered by exercise and other clinical maneuvers commonly employed for their differentiation.

Of particular interest to us has been the finding that, with suitable equipment, functional systolic murmurs may be recorded from the precordium of virtually all normal subjects at rest.

Method and Procedure

Two instruments utilized in this study have been previously described:[3] a nonacoustical type of pickup for electronic reproduction of sounds from the precordium, and a soundproof room. The necessity for the latter, in this case a 10,000 pound steel and fiber-glass structure in which no ex-

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traneous noise is audible to the human ear, has been indicated by an earlier study[4] demonstrating the role played by commonly encountered levels of background noise in determining the audibility of heart murmurs. All recordings were made on a double beam cathode-ray oscilloscope located outside the soundproof room, one channel displaying the sounds and the other the subject's electrocardiogram for purposes of timing in the cardiac cycle. Technical details of the method have been set forth in previous publications.[3, 5]

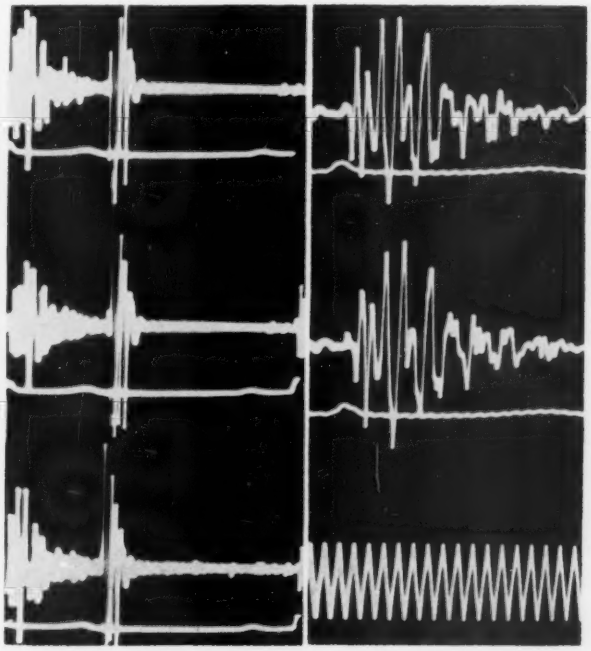

FIG. 1. Three consecutive sound tracings from a single area of precordium of a subject (left), each showing one heart cycle with its simultaneously recorded electrocardiogram. At the right are two "magnified" views of systole of the same subject (made by increasing the speed of the horizontal "X" axis of the oscilloscope), showing the first heart sound and the decrescendo murmur in detail. The triangular wave form (bottom right) is a 50 c.p.s. time marker.

Recordings were made consecutively on 71 normal adult subjects. They ranged in age from 20 to 51, and three-fourths of them were males, mostly students and medical staff of this institution. Criteria for selection were simply that they have no known cardiovascular abnormality and, in particular, that they have no history suggestive of heart disease or of a detection of murmur on any previous examination. Any individual in whom a murmur was audible on ordinary stethoscopic examination was rejected. Each

subject was recorded in the soundproof room, at rest and recumbent, with respiration suspended at approximately mid-phase. Multiple recordings were made on each subject to ascertain the degree of reproducibility of the tracing and to locate the point of maximal intensity on the precordium.

A second phase of the study entailed the recording of fetal heart sounds from the maternal abdomen during the last trimester of gestation. Essentially the same methods were employed, except that the maternal electrocardiogram was recorded with the fetal sounds both as an indicator of fetal heart rate and to demonstrate lack of synchronism between the two.

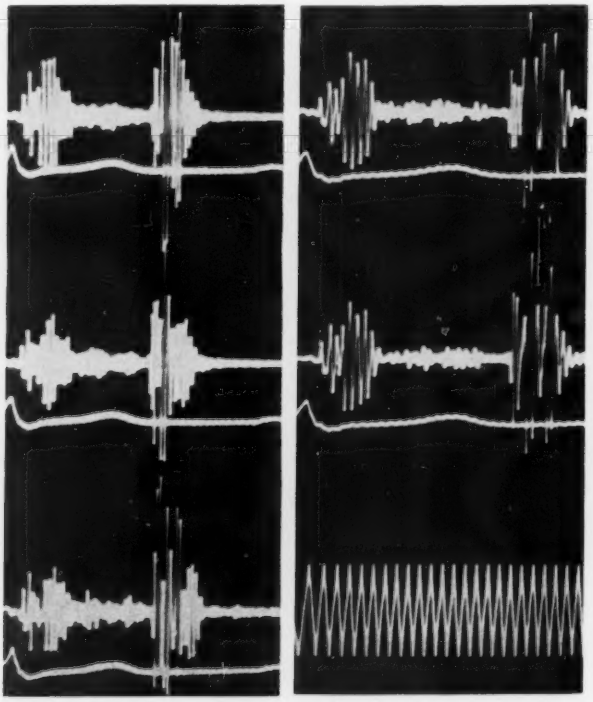

FIG. 2. Tracings of another normal adult, arranged as in Figure 1, showing a somewhat diamond-shaped (though variable) systolic murmur, with a brief interval of silence immediately before the second heart sound. Note the marked splitting of the second sound, seen best in the detail views of systole on the right.

RESULTS

Utilizing this technic, adjusting the pickup for maximal sensitivity and exploring several areas of the precordium, we found systolic murmurs in the tracings of all 71 normal subjects. That these adventitious sounds were not artifacts or simply prolongations of the first heart sound was evident

from the fact that all occupied one-fourth or more of systole and were reproducible in repeated recordings. In four of the subjects a murmur was detected on the first attempt only after elevation of the feet or various changes in phase of respiration, hyperventilation or mild exercise, and in another none was evident with any of these maneuvers at first; but systolic

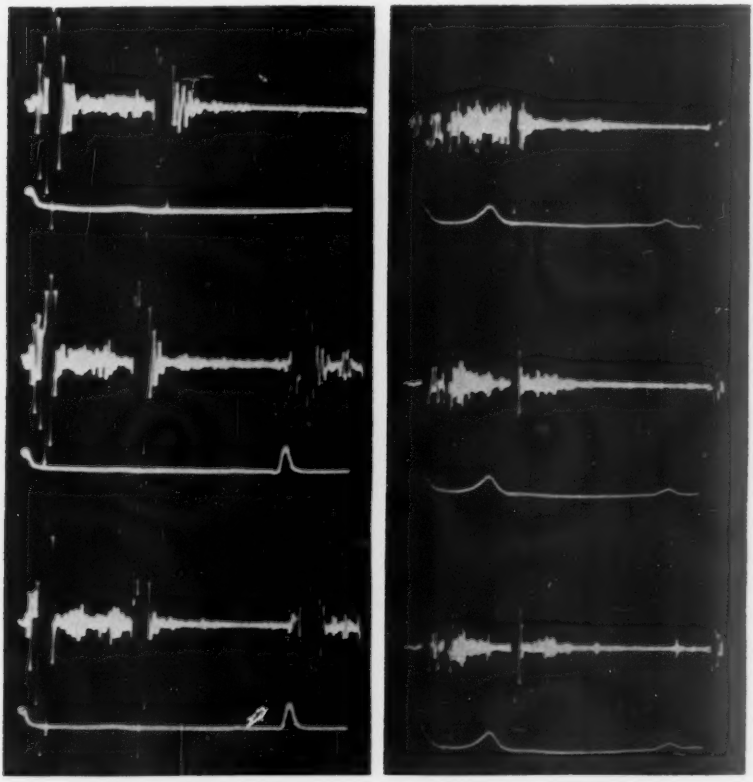

FIG. 3. Three consecutive recordings from one subject (left) and another (right), illustrating variability of the systolic murmurs with small physiologic variables, the locations on the precordium remaining unchanged. Diastolic sounds are particularly evident in the tracings on the right.

murmurs were easily demonstrated in the same subjects when the recordings were repeated several days later at complete rest. Such maneuvers were observed to influence the intensity and even the configuration of the murmurs but they were not routine procedure and, in the vast majority of subjects, the findings described were recorded readily on the first attempt.

Classification of the precordial murmurs in terms of pattern is difficult, at best. A predominantly decrescendo configuration was observed in the

tracings of 58% of the subjects (figure 1), the murmur beginning with the first heart sound and extending through part or all of systole. Most of this type were recorded along the lower left sternal border or near the apex of the heart, and about half of them extended throughout systole. At least some semblance of a diamond-shaped pattern was observed in about 25% of the murmurs, especially those recorded near the base of the heart (figure

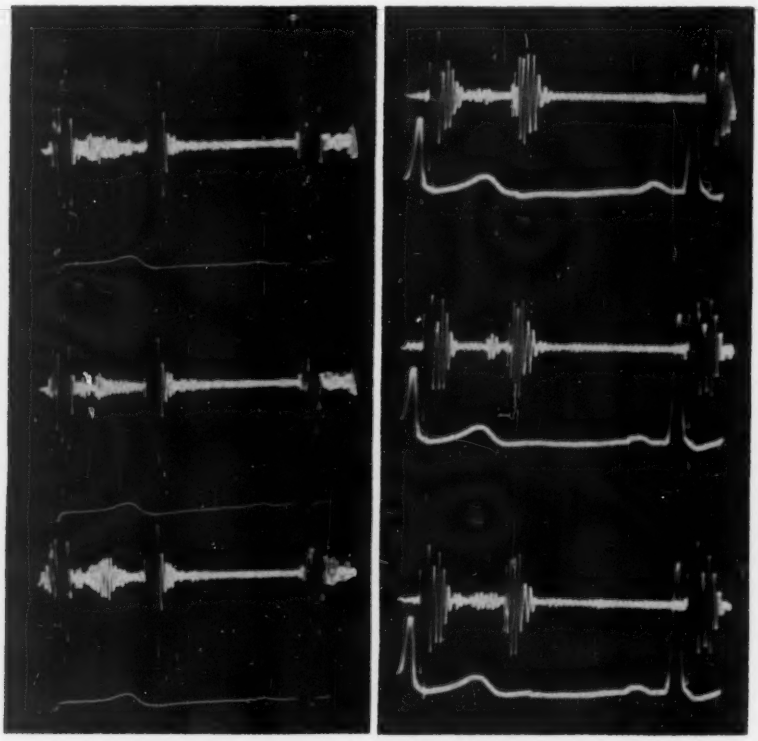

FIG. 4. Precordial recordings from two subjects, showing variability in intensity and pattern of murmurs, and the remarkably simple wave forms comprising the murmurs, which had a musical quality.

2). The remaining 17% of the 71 subjects showed murmurs which apparently were combinations of these, or were of more or less uniform intensity throughout systole, or were so variable as to defy classification by contour. In fact, variability in shape and intensity from one heart cycle to another, and with minor changes in position or in phase of respiration, was a prominent feature in many of the recordings, and is illustrated in figures 3, 4 and 5. It should be noted that no attempt was made to record any particular type of murmur in the subjects; the pickup was positioned on the pre-

cordium to obtain the maximal intensity of murmur in systole, irrespective of its configuration. These are the locations plotted in figure 6, though murmurs of other shapes may have been evident at other precordial locations of many of the subjects.

More detailed scrutiny of the precordial murmurs by means of electronic expansion of the tracings and measurement of the waves against a time

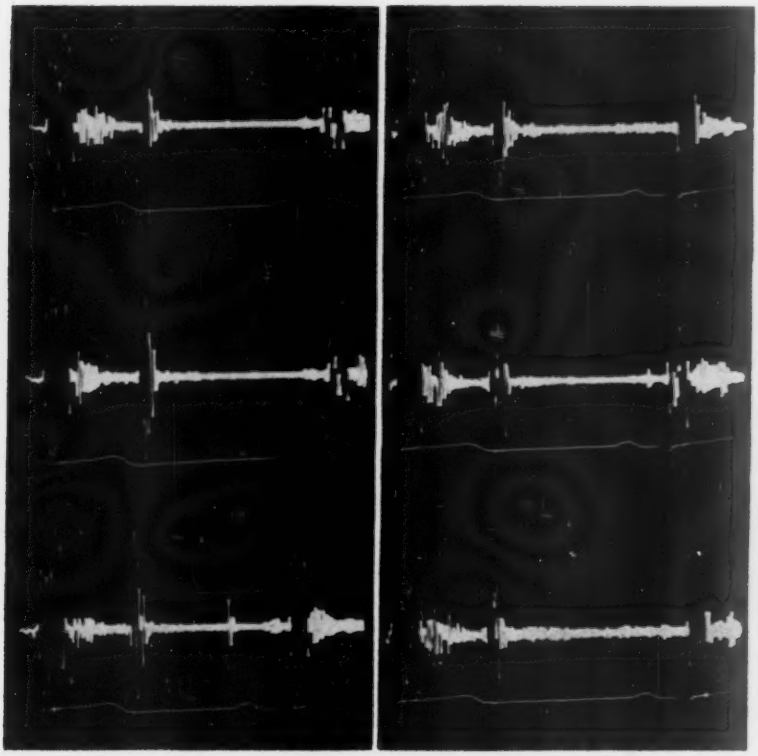

FIG. 5. Six consecutive recordings from the same patient on a single site on the precordium. Note the vestige of the fourth heart sound which immediately follows the P wave. The short click in diastole (lower left) is unexplained.

marker of known frequency revealed the majority of them to have a basic or fundamental frequency on the order of 60 to 90 cycles per second, with secondary frequencies perhaps an octave or more higher. Sinusoidal wave forms were prominent in about two-thirds of the murmurs. These regular oscillations, signifying a sound of musical quality, may well be a prime characteristic of such functional murmurs, and they contrast remarkably with the seemingly random mixture of many frequencies in the "noise" patterns of most pathologic murmurs.

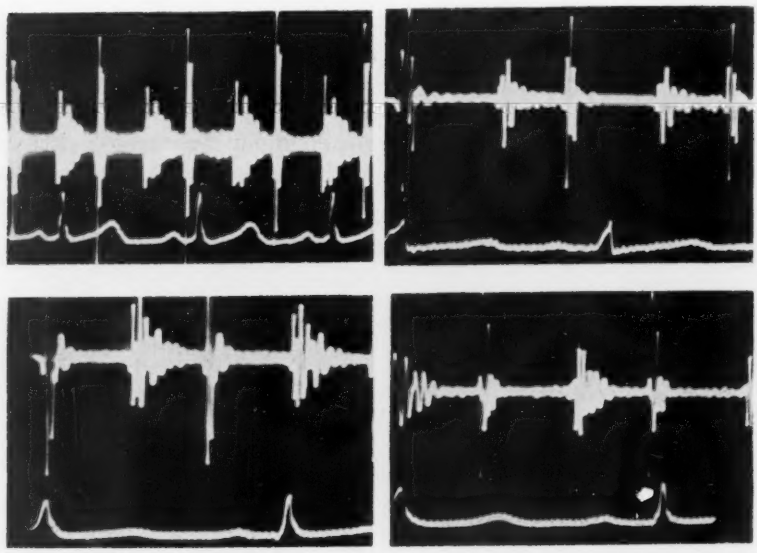

FIG. 6. Fetal heart sounds of four separate subjects. The maternal electrocardiogram is shown below each. A murmur was considered to be doubtful in the lower right tracing.

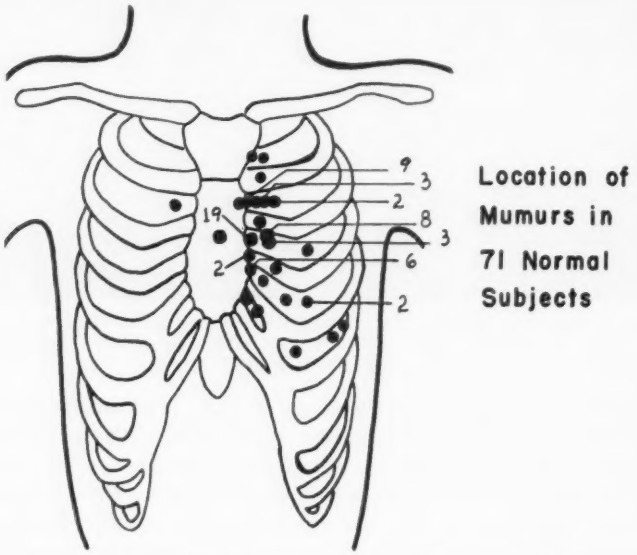

FIG. 7. Approximate locations of maximal intensity of murmurs. The numerals signify the numbers of subjects recorded at a given location (e.g., in 19 subjects the point of maximal impulse was in the third intercostal space at the left sternal border).

Diastolic sounds of much lower intensity, and confined mainly to the first third or half of diastole, were found in approximately one-fourth of the subjects. How many of these can qualify as murmurs (figure 3), and how many might more properly be called after-vibrations or splitting of the second heart sound (figure 2), is open to question. Some degree of splitting of the second sound was a common finding, as were vestiges of the third and fourth heart sounds which are readily recorded in normal subjects by low frequency pickups, but were largely eliminated from these tracings by filtering.

In the obstetrical series, 19 of the 25 patients recorded during the last trimester of pregnancy had what were construed as definite fetal heart murmurs. As judged by the tracings (figure 7), they were systolic in time, and almost invariably their pattern was a decrescendo one. The six subjects in whom the murmur was considered to be doubtful or absent were not recorded again later, although experience suggested that success in demonstrating the murmurs was dependent upon how meticulously one explored the maternal abdomen with the pickup and how quiet were the maternal bowel sounds. Subsequently, physical examinations of the infants in the nursery did not disclose any congenital cardiovascular anomalies.

Discussion

Several features of these systolic sounds in the adult fit closely those generally regarded as typical of functional systolic murmurs: their prominent variation with changes in position, respiration and other physiologic variables, their variability from day to day, their usual location along the lower left sternal border, perhaps the relative prominence of sinusoidal wave forms, and of course their extremely low intensity. It appears that they represent a universal phenomenon of normal circulation. At times they may become audible on auscultation, but more often they are not—unless one listens in a completely quiet environment such as a soundproof room, and even then it is often difficult to discern them with certainty, knowing they are present. Quite likely these are the sounds which, when of sufficient intensity at the chest wall, are heard during physical examinations of some normal subjects and interpreted as functional systolic murmurs. The significant finding of this study is that they were recorded from the precordium of all of the normal subjects, irrespective of age, sex, or thickness or resilience of the chest wall. (Similar murmurs are found under very adverse conditions of transmission such as those illustrated in the patients of figure 8, in whom the heart sounds themselves were almost completely inaudible by auscultation.) Requisites for their recording are a system of high sensitivity and a sufficiently low level of ambient noise.

A semantic question might be raised as to whether these are really murmurs, if the term "murmur" by definition denotes a sound which can be heard. The frequencies involved are well within the range of human

audibility (and stethoscopic transmission) but the ear is a relatively insensitive detector below 100 cycles per second,[6] particularly at low intensity levels. Were a greater proportion of higher frequencies intermixed in the sounds, their "loudness" would be greater. However, stethoscopic audibility of a murmur is also dependent upon factors other than the intensity or the nature of the sound itself.[7] From a practical standpoint, there is no single threshold level of audibility; rather, the threshold is directly related to the acuity of the listener or the capabilities of the instrumentation employed, as well as to the conditions under which the observation is made. Graphically these sounds fit our criteria of murmurs. And, after all, there is no valid reason to believe that all murmurs of significance—physiologic or pathologic—should necessarily be audible to the human ear with our present method of clinical auscultation.

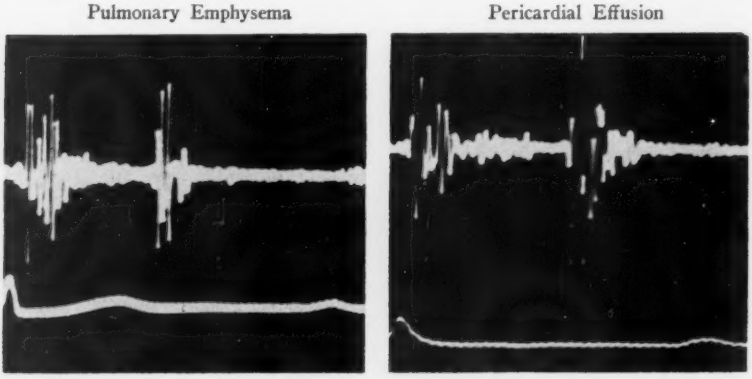

FIG. 8. Tracings from two patients in whom heart sounds were barely audible by auscultation: an elderly man with a "barrel chest," and a 28 year old man with massive pericardial effusion. Neither patient had evidence of any valvular heart disease.

One is tempted to classify the patterns of the precordial sounds according to "regurgitant" or "ejection" mechanisms of origin. But from these preliminary observations, such classification would be little more than conjecture. Furthermore, present criteria[8] for the two categories are based chiefly on pathologic murmurs, which may or may not be analogous in origin to these normal sounds. While the diamond-shaped patterns are strongly suggestive of ejection phenomena, the origin of the more commonly encountered decrescendo configuration, following immediately upon the first heart sound without an intervening silent interval, is less certain. It appears probable that more than a single type of murmur is present—at least in many of the subjects—and that various mixtures or combinations of two or more sounds were recorded in seeking the point of maximal intensity on the precordium. Understandably, the normal flow of blood through the irregular contours of the heart and great vessels might generate vibrations

and sounds which would be of greater intensity during systole because of the higher pressures involved. Adequate evidence with which to explain the origin and mechanisms of these sounds is lacking, however, and awaits further investigation.

The fetal circulation is of course entitled to a murmur, if only because of its functioning ductus arteriosus and foramen ovale. A simultaneous fetal electrocardiogram would be desirable to prove that it is systolic, though presumably it is. More surprising, perhaps, than the presence of such murmurs is the fact that they are rarely heard clinically, due probably to the small size of the fetal structures, the doubtless lower circulatory pressures, and the comparatively large mass of intervening fluid and maternal tissues. At one time it was believed that congenital cardiovascular anomalies in the fetus could be diagnosed before birth by the detection of a fetal heart murmur,[9] but certainly much further study of the normal fetal sounds is necessary before that goal can be achieved.

Summary

The presence of functional systolic murmurs in some adults has long been recognized. Of recent interest is the finding that these murmurs can actually be recorded from the precordium in virtually all normal subjects.

By means of a high sensitivity capacitance pickup in a soundproof room, recordings were made on a cathode-ray oscilloscope from 71 normal adult subjects. Only those with a negative past history of a murmur or heart disease were included, and in none of them was a murmur audible on ordinary stethoscopic examination. Recordings were made with the subject at rest in the supine position.

All subjects showed readily discernible murmurs extending through one-fourth or more of systole, and reproducible on repeated tracings. In more than three-fourths of the subjects the point of maximal intensity was between the second and fourth intercostal spaces along the left sternal border. Wave forms of most murmurs showed some sinusoidal characteristics, with fundamental frequencies of 60 to 90 cycles per second, and secondary frequencies an octave or more higher. The majority of the murmurs were of decrescendo configuration following the first heart sound; only about one-third had a diamond-type pattern and some appeared to be combinations of these two. Their intensity tended to vary from day to day, with different phases of respiration or changes in position, and with exercise. Short diastolic sounds were recognizable in the tracings of a few of the subjects.

With the same technic, murmurs were found in 19 of 25 fetal hearts recorded during the last trimester of gestation. Presumably the fetal murmurs are systolic in time, and arise from shunts unique to the fetal circulation.

The mechanism and site of origin of these systolic sounds in the adult are uncertain. However, their presence is understandable on the basis of

what is known of circulatory dynamics, and it appears that they represent a universal functional murmur which is usually subaudible.

SUMMARIO IN INTERLINGUA

Le presentia de functional murmures systolic in certe adultos es cognoscite depost longe tempore. De interesse special es le plus recente constatation que tal murmures pote de facto esser registrate ab le precordio de virtualmente omne subjectos normal.

Per medio de un alterubi describite pickup de altissime sensibilitate in un camera insonorisate, registrationes esseva obtenite ab 71 normal subjectos adulte in un oscilloscopio a radios cathodic. Esseva includite in le serie solmente patientes con un historia negative de murmure o morbo cardiac. Murmures esseva audibile in nulle de illes in ordinari examines stethoscopic. Le registrationes esseva effecuate con le subjectos in stato de reposo in position supin.

Omne le subjectos revelava prestemente discernibile murmures con un extension a transverso un quarto o plus del systole, e iste murmures esseva reproducibile in repetite registrationes. In plus que tres quartos del subjectos studiate, le puncto de intensitate maximal del murmures esseva inter le secunde e le quarte spatio intercostal al longo del margine sinistro-sternal. Le forma del unda in le majoritate del murmures exhibiva alicun characteristicas sinusoide con frequentias fundamental de 60 a 90 cps e frequentias secundari superior per un octava o plus. Le majoritate del murmures habeva un configuration de decrescendo post le prime sono cardiac; solmente circa un tertio habeva un configuration del typo rhomboide; certes pareva representar un combination del duo. Le intensitate tendeva a variar ab un die al altere, in differente phases de respiration, in differente positiones, e sub le influentia de exercitios. Curte sonos diastolic esseva recognoscibile in le registrationes de un certe numero del subjectos.

Con le uso del mesme technica, murmures esseva trovate in 19 inter 25 cordes fetal studiate durante le ultime trimestre del gestation. Il es probabile que le murmures fetal es systolic quanto a lor occurrentia in le cyclo cardiac e que illos ha lor origine in shuntings que es characteristicas specific del circulation fetal.

In le adultos, le mechanismo e le origine del hic discutite sonos systolic es incerte. Tamen, lor presentia es comprensibile super le base del factos cognoscite con respecto al dynamica circulatori. Il pare que illos representa un murmure functional universal que es usualmente inaudibile.

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PHONOCARDIOGRAPHY IN PULMONARY STENOSIS: SPECIAL CORRELATION BETWEEN HEMODYNAMICS AND PHONOCARDIOGRAPHIC FINDINGS *

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This investigation was carried out to appraise the value of auscultatory and phonocardiographic findings as clinical tools for estimating the degree of severity of pulmonary stenosis, with or without intracardiac shunt. The value of phonocardiography in these conditions has been the subject of some controversy.[1,2]

Material and Methods

Fifty-six patients with pulmonary valvular or infundibular stenosis were subjects of this study. The clinical impression was confirmed by cardiac catheterization in all cases, and in 21 cases by operation or postmortem examination as well.

Twenty-one cases of pulmonary stenosis without evidence of intracardiac shunt, 30 cases of pulmonary stenosis with ventricular septal defect, including tetralogy of Fallot, and five cases of pulmonary stenosis with interatrial communication formed the basis of this study.

The Twin-Beam Sanborn phonocardiography machine was used in every case. In some cases presenting special diagnostic problems a four-channel Visocorder (Honeywell), modified for sound recordings, was used. All tracings were taken at the speed of 75 mm. per second.

Logarithmic recording technic for an accurate analysis of high frequency sound was used in all cases.[1,2,3] The stethoscopic recording technic was used in addition to logarithmic recording at the apex and pulmonic areas to detect low frequency sounds, such as third and fourth sounds, and the soft pulmonic component of a split second sound.

The sound tracings were recorded at the apex, left sternal border at the third and fourth intercostal spaces, pulmonary and aortic areas.

Electrocardiographic tracings were used to identify the atrial sound.

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The carotid artery tracing, jugular venous tracing and apexcardiogram were recorded simultaneously with the phonocardiogram, using a crystal piezoelectric microphone Sanborn pickup. In the great majority of cases, two simultaneous sound tracings in different precordial areas were also obtained. The tracings were analyzed in the usual fashion, but special attention was given to the splitting of the second sound, duration and contour of a systolic murmur, and duration of right ventricular systole. The components of the split second sound were identified by their relation to the dicrotic notch of the carotid tracing. The aortic component usually preceded the dicrotic notch by 0.03 second (pulse wave transmission from the aortic valve to the carotid artery). The pulmonary component of the second sound was recognized by its occurrence after the dicrotic notch and by its increased intensity at the pulmonic area. Simultaneous phonocardiograms at the mitral and pulmonic areas also helped to identify it. In cases with a widely split second sound, the pulmonic component of the second sound might have been mistaken for the right ventricular third sound. A jugular venous tracing was therefore used to differentiate the two. If the sound occurred before the peak of "v" wave, it was assumed that it was due to pulmonic valve closure, but if it occurred after the apex of the "v" wave it was assumed to be the third heart sound. The third sound coming from the left ventricle is not usually transmitted to the pulmonic area.[16]

Apexcardiograms of the right and left ventricles were also used to differentiate the third heart sound from the widely split second sound. If the sound occurred at the peak of rapid filling wave it was assumed to be a third heart sound.

We used the criteria of Leatham and Vogelpoel [4] to identify the systolic ejection click (S.E.C.).

The duration of right ventricular systole was determined from simultaneous tracings taken at the tricuspid and pulmonic areas. The interval was calculated from the tricuspid component of the first sound at the tricuspid area to the pulmonic component of the second sound at the pulmonic area.

The right ventricular and pulmonary artery pressures were determined during routine right heart catheterization, using a Statham Strain Gauge with the zero point at one-half the chest diameter at the sternal angle.

Patients were placed in three groups arbitrarily, determined by the degree of right ventricular pressure, as follows:

Mild pulmonary stenosis: pressure between 35 and 60 mm. Hg
Moderate pulmonary stenosis: pressure between 60 and 110 mm. Hg
Severe pulmonary stenosis: pressure above 110 mm. Hg

An estimate of the right ventricular work is available by applying the following formula.[26, 31, 32, 33, 34]

$$RV_w = \frac{PF \times (RVm - RAm) \times 13.6 \times 1.05}{1000} = \text{Kg. M./min./m}^2$$

RV_w = work of right ventricle against pressure
PF = pulmonary flow, liters per minute
RV_m = right ventricular mean pressure, mm. Hg
RA_m = right auricular mean pressure, mm. Hg
13.6 = specific gravity of mercury
1.05 = specific gravity of blood
normal RV_w = 0.5 to 1.1 Kg. M./min./m^2 [31]

Results

Pulmonary Stenosis without Shunt: Twenty-one cases of isolated pulmonary stenosis were studied. The first sound was normal in all cases, and was followed by a systolic ejection click in five. There was a correlation between the right ventricular pressure and the time interval from the mitral component of the first sound to the systolic ejection click.

The systolic ejection click was recorded only in mild and moderate cases of pulmonary stenosis. As the right ventricular pressure increased, the ejection click tended to be closer to the first sound. The second sound was diminished and abnormally split in all cases. The width of splitting during expiration varied between 0.04 to 0.12 second. Figure 1C shows that the time interval of the split second sound increased as the pressure gradient across the pulmonary valve increased. This relationship occurs in an almost linear fashion.

The pulmonic component of the second sound was not recorded in six cases. The right ventricular pressure was higher than 80 mm. of Hg in all of these cases. The absence of the pulmonic component seemed to indicate moderate to severe pulmonary stenosis (figure 2).

The normal right ventricular systole as we determined it in 25 normal people ranged from 0.29 to 0.32 second, with an average of 0.30. The duration of right ventricular systole in the pulmonary stenosis group ranged between 0.32 to 0.41 second, with an average of 0.35 second. The duration of right ventricular systole increased in proportion to the degree of right ventricular hypertension.

Right ventricular work was determined in eight cases by the formula indicated above, and it was considered to be increased in four cases. Right ventricular systole was prolonged in cases in which the right ventricular work was greater than 1.1 Kg.M/min./m^2 (figure 1A).

A loud systolic ejection murmur was recorded in all cases. The time interval between the start of the murmur and the mitral first sound was about 0.02 second. This murmur showed early and midsystolic accentuation in the majority of cases of mild and moderate stenosis. However, in severe stenosis the murmur was late systolic in accentuation (table 1, figures 2 and 3).

Tall or giant "a" waves were recorded in the jugular venous pulse in nine cases, and correlated with the degree of right ventricular pressure but not with the degree of right auricular pressure (figure 4). In all of them the right ventricular pressure was higher than 90 mm. Hg.

In three cases the diagnosis of infundibular stenosis with distinct infundibular chamber could be made by cardiac catheterization. In two of these cases the murmur ended at the aortic component of the second sound.

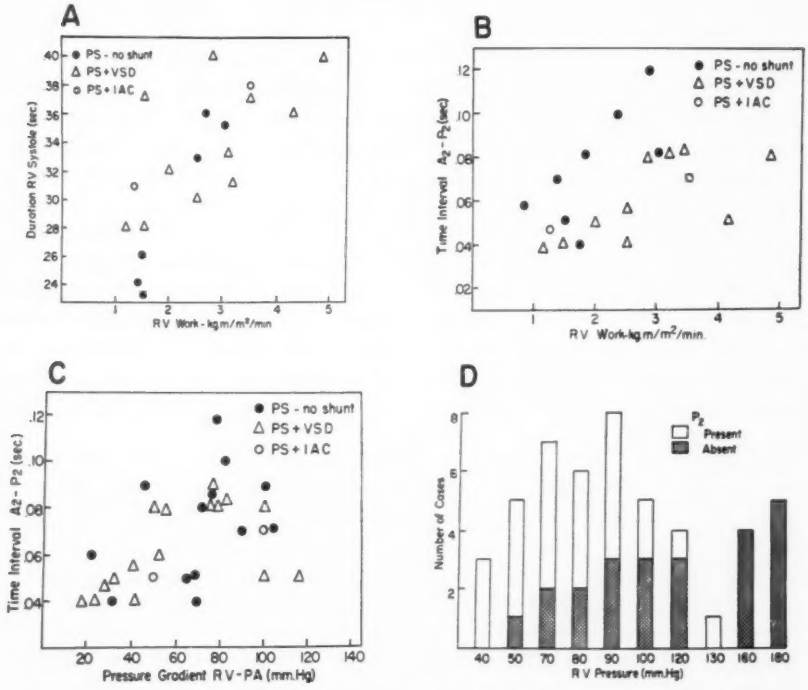

FIG. 1. (a) Relation between the duration of right ventricular systole and the right ventricular work. (b) Relation between the width of splitting of second sound (A_2-P_2 interval) and the right ventricular work. (c) Relation between the width of splitting of second sound (A_2-P_2 interval) and the pressure gradient across the pulmonary valve. (d) Relation of presence or absence of pulmonic component of the second sound with right ventricular pressure.

A fourth sound was recorded in nine cases and correlated well with the degree of right ventricular pressure, which was higher than 80 mm. Hg in all of them.

A third sound was present in five cases, and in all of them the degree of stenosis was moderate to severe. Right ventricular pressure in these cases was higher than 90 mm. Hg.

TABLE 1

Time of Accentuation of Systolic Murmur in Relation to the Severity of Stenosis

Time Accentuation Systolic Murmur	*PS—No Shunt						†PS + VSD						‡PS + IAC					
	Mild, No. Cases	(%)	Moderate, No. Cases	(%)	Severe, No. Cases	(%)	Mild, No. Cases	(%)	Moderate, No. Cases	(%)	Severe, No. Cases	(%)	Mild, No. Cases	(%)	Moderate, No. Cases	(%)	Severe, No. Cases	(%)
Early	1	(5)	—	—	—	—	1	(3)	2	(7)	—	—	—	—	1	(20)	—	—
Early + Mid	1	(5)	—	—	—	—	2	(7)	5	(17)	1	(3)	—	—	—	—	—	—
Mid	1	(5)	4	(18)	—	—	2	(7)	8	(27)	2	(7)	—	—	—	—	—	—
Mid + Late	1	(5)	4	(18)	5	(23)	—	—	2	(7)	2	(7)	—	—	2	(40)	1	(20)
Late	—	—	2	(7)	2	(7)	—	—	—	—	2	(7)	—	—	—	—	1	(20)

* Isolated pulmonary stenosis.
† Pulmonary stenosis and ventricular septal defect.
‡ Pulmonary stenosis and interatrial communication.

Pulmonary Stenosis with Ventricular Septal Defect: In this group of 30 we included patients with pulmonary stenosis plus ventricular septal defect, with or without overriding aorta. Therefore, cases of tetralogy of Fallot showing cyanosis early in life were included in this group. Angiocardiograms, operation and occasionally postmortem examination confirmed the septal defect.

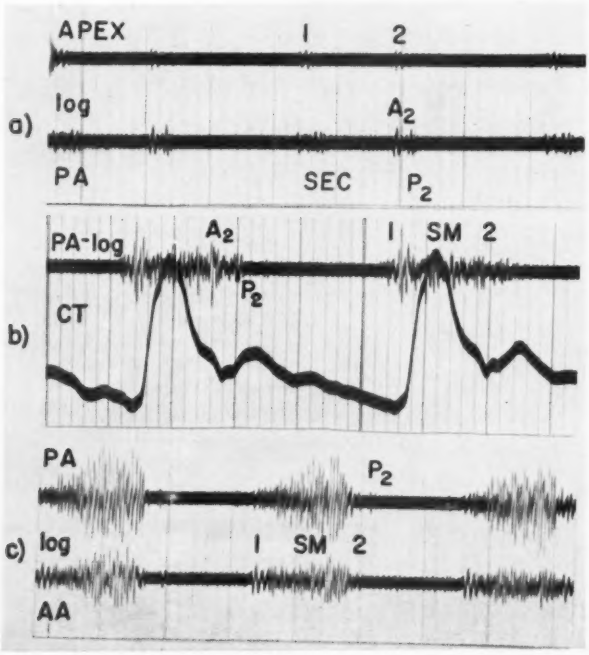

FIG. 2. (a) Mild isolated pulmonary stenosis. Second sound shows a split of 0.05 sec. and the pulmonic component is normal. A systolic ejection click is present. RV pressure, 45/0 mm. Hg. PA pressure, 18/10 mm. Hg. Low amplitude systolic murmur with early and midsystolic accentuation. (b) Moderate isolated pulmonary stenosis. RV pressure, 70/0 mm. Hg. PA pressure, 13/8 mm. Hg. Systolic ejection murmur going through the aortic component of the second sound, which is split to 0.08 sec. (c) Severe isolated pulmonary stenosis. RV pressure, 200/0 mm. Hg. PA pressure, 13/6 mm. Hg. Systolic murmur with late systolic accentuation. Second sound is widely split (0.08 sec.), and the pulmonic component is markedly diminished.

In 11 cases out of 30 the dominant shunt determined by cardiac catheterization was right-to-left. The other 19 cases did not have peripheral desaturation.

The first sound was considered to be normal in all of them, and was followed by a systolic ejection click in only five cases. In three of these the shunt was predominantly left-to-right, and in the other two was right-to-left.

The third sound was recorded in 11 patients with moderate and severe

pulmonary stenosis, and the right ventricular pressure was higher than 80 mm. Hg. A fourth sound was present in 11 cases, all of whom had right ventricular pressures greater than 90 mm. Hg (figure 5).

The second sound at the pulmonic area, when present, was widely split, and the pulmonic component was diminished in all cases. In cases with a dominant right-to-left shunt the pulmonic component, although diminished, could be well delineated in four cases, and was not recorded in nine. In 14 cases with dominant left-to-right shunt the pulmonic component of the second sound was diminished but present in nine and absent in five (figure 6).

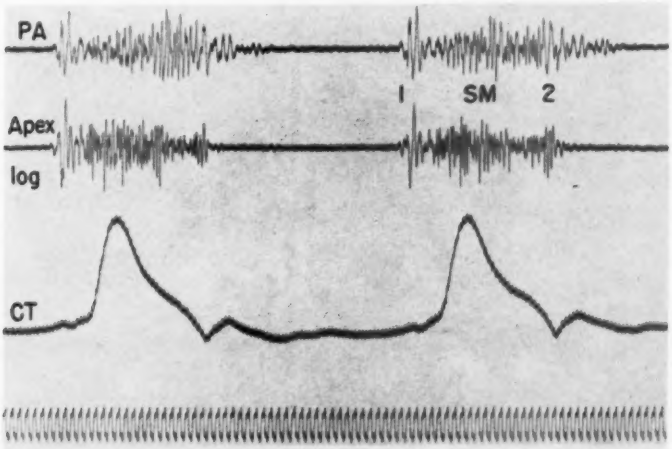

FIG. 3. Severe isolated pulmonary valvular stenosis. RV pressure, 150/0 mm. Hg. PA, 18/10 mm. Hg. Systolic ejection murmur extending through the aortic component of second sound. Pulmonic component of second sound is absent.

The duration of the split maintained a good correlation with the pressure gradient across the pulmonary valve (figure 1C). In all cases in this group in which the pulmonic component was absent, the right ventricular pressure was higher than 80 mm. Hg.

A high amplitude, high-pitched systolic murmur, more intense at the pulmonary area and starting on an average of 0.03 second after the first sound, was recorded in all cases. In cases of mild or moderate stenosis the murmur showed an early or midsystolic accentuation. In cases of severe stenosis in which the right ventricular pressure was higher than 110 mm. Hg, the murmur showed late systolic accentuation (table 1).

In the group of patients with dominant right-to-left shunt, the murmur ended before or at the aortic component in five cases and went through the aortic component in six cases (figure 6).

No difference in the onset of the murmur could be noted between patients with tetralogy of Fallot and patients with pulmonary stenosis plus ventricular septal defect and left-to-right shunt. In five cases of tetralogy of Fallot, an early diastolic murmur was recorded at the apex and left sternal border areas.

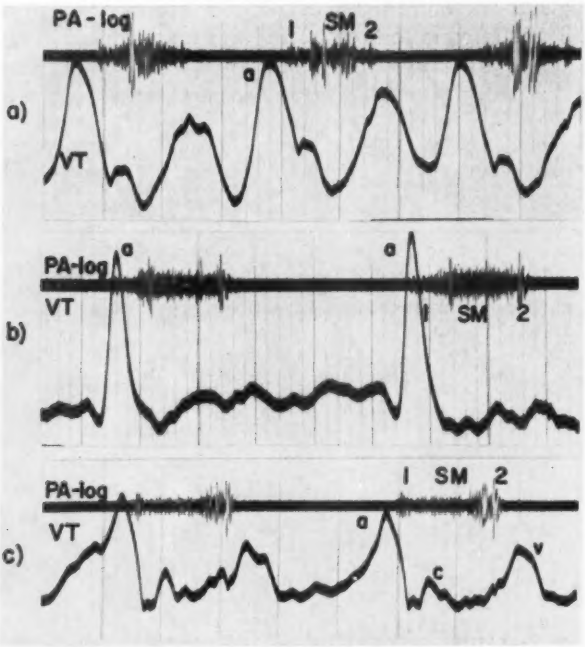

FIG. 4. (a) Moderate isolated pulmonary valvular stenosis. Jugular venous tracing shows prominent "a" waves. RV pressure, 60/0 mm. Hg. PA, 10/5 mm. Hg. Pulmonic component of second sound is absent. Systolic ejection murmur ending at the aortic second sound. (b) Severe isolated pulmonary valvular stenosis. RV pressure, 175/0 mm. Hg. PA pressure, 15/12 mm. Hg. Giant "a" waves in the jugular venous pulse. P_2 is absent. Systolic ejection murmur stopping at the aortic second sound. (c) Severe pulmonary infundibular stenosis with atrial septal defect and bidirectional shunt. RV pressure, 150/0 mm. Hg. PA pressure, 18/7 mm. Hg. Somewhat prominent "a" waves in the venous tracing. Systolic ejection murmur with late systolic accentuation ending at the aortic second sound. P_2 is absent.

In 13 cases an infundibular chamber was predicted during cardiac catheterization, and in seven of these cases the diagnosis was confirmed by necropsy or operation. In eight cases of the 13 the murmur ended before or at A_2, and went through the aortic component in five cases.

The jugular tracing showed giant "a" waves in only two cases, and prominent "a" waves in eight. Again, the right ventricular pressure was markedly elevated in both conditions, being an average of 118 mm. Hg with giant "a" waves, and 100 mm. Hg in cases with prominent "a" waves.

Pulmonary Stenosis with Interatrial Communication: There were five patients in this group. With the exception of one subject who had left-to-right shunt, all showed central cyanosis with right-to-left shunt at the atrial level. These patients had severe pulmonary stenosis, and, owing to the presence of marked elevation of right ventricular and auricular pressure, the shunt was reversed at the atrial level through an atrial septal defect or patent foramen ovale.

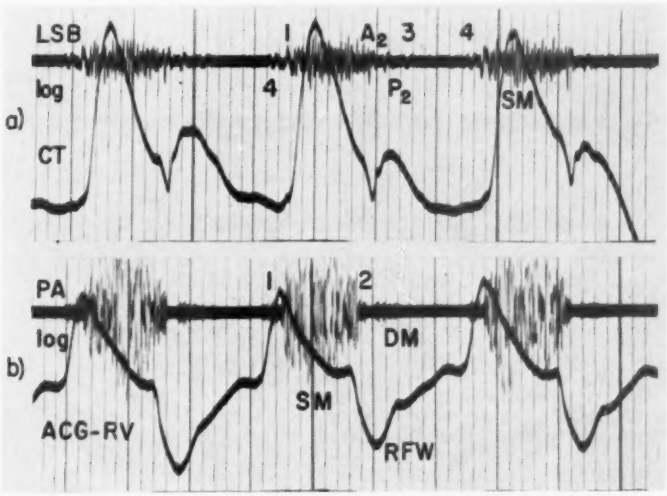

FIG. 5. Pulmonary infundibular stenosis with ventricular septal defect and dominant right-to-left shunt. RV pressure, 90/0 mm. Hg. Infundibular chamber, 56/0 mm. Hg. PA pressure, 25/5 mm. Hg. (a) Systolic murmur showing mid- and late systolic accentuation and ending at the aortic component of second sound. Third and fourth sounds recorded at LSB. (b) High-pitched diastolic murmur at the pulmonary area with maximal intensity at time of rapid filling phase of right ventricular apexcardiogram.

It was impossible to differentiate these patients by auscultation or phonocardiography from the group with isolated pulmonary stenosis. They consistently showed a widely split second sound, a diminished or absent pulmonic component, and prolongation of right ventricular systole. The systolic murmur usually showed late systolic accentuation, occasionally extending through the aortic component of the second sound (table 1). The fourth heart sound was present in four cases, and the jugular tracing showed giant "a" waves in all of them (figure 7).

DISCUSSION

The auscultatory and phonocardiographic findings in pulmonary stenosis correlated well with the altered hemodynamics. Obstruction at the pul-

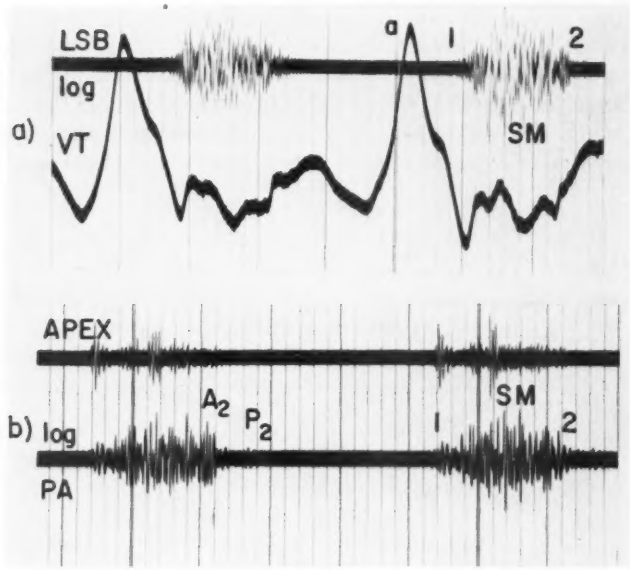

FIG. 6. Severe pulmonary stenosis with ventricular septal defect and right-to-left shunt (tetralogy of Fallot). RV pressure, 100/0 mm. Hg. PA pressure, 35/12 mm. Hg. (a) Systolic ejection murmur ending at the pulmonic component of second sound, which is markedly diminished. Jugular venous tracing shows giant "a" waves. (b) Simultaneous sound tracing at the apex and pulmonary area showed a widely split second sound (0.09 sec.).

monic valve or outflow tract level produced an increase in the duration of right ventricular systole. The delayed closure of the pulmonary valve produced a widely split second sound. The width of the split was proportional to the severity of the stenosis. The low pulmonary diastolic pressure may also have contributed to this delay. The splitting of the second sound in

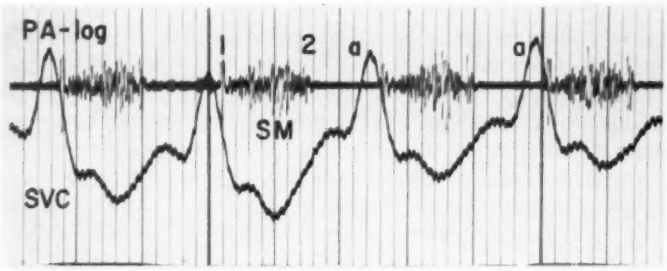

FIG. 7. Severe pulmonary valvular stenosis with reversed shunt at atrial level. RV pressure, 150/6 mm. Hg. PA pressure, 11/6 mm. Hg. The venous tracing taken during cardiac catheterization with the catheter tip at superior vena cava shows giant "a" waves. Systolic ejection murmur ends at aortic component of second sound.

TABLE 2

Summary of Phonocardiographic Findings; Differential Diagnosis of Isolated Pulmonary Stenosis from Pulmonary Stenosis + Intracardiac Shunt

Phonocardiographic Findings	Isolated Pulmonary Stenosis			PS + IAC	PS + VSD*
	Mild	Moderate	Severe		
Systolic ejection click	Usually present	Uncommon	Uncommon	Uncommon or absent	Uncommon or absent
Pulmonic second sound	Present, normal	Present and diminished	Diminished or absent	Absent	Uncommon or absent
Time interval, A_2-P_2	.03 to .05	.04 to .08	.05 to .12	When P_2 present, .06 to .12	When P_2 present, .06 to .12
Aortic second sound	Normal	Normal	Normal	Normal	Accentuated or normal
Time of accentuation of systolic murmur	Early	Mid	Late	Late	Mid or late
End of systolic murmur	Before A_2	At A_2	Through A_2	Ends at A_2	Ends at A_2; may go through A_2
Diastolic murmur	Absent	Absent	Absent	Absent	Fairly common
Third and fourth heart sounds	Absent	Uncommon	Common	Uncommon	Common
Right ventricular systole	Normal	Slightly prolonged	Markedly prolonged	When P_2 present, markedly prolonged	When P_2 present, moderately prolonged
Venous tracing—"a" wave	Normal	Tall	Giant	Tall or giant	Normal or tall

* Including tetralogy of Fallot.

pulmonary stenosis has been recognized by many others as a valuable diagnostic sign in this condition.[5, 6, 7, 8, 9, 24, 25, 27, 28, 35] A prolonged systolic murmur which extends beyond the aortic component of the second sound and ends at the pulmonic component can be detected by phonocardiography.

The resistance to blood flow produced by the stenotic pulmonary valve causes an increase in duration of right ventricular systole to allow the entire stroke volume to be ejected. This is accompanied by a powerful late ven-

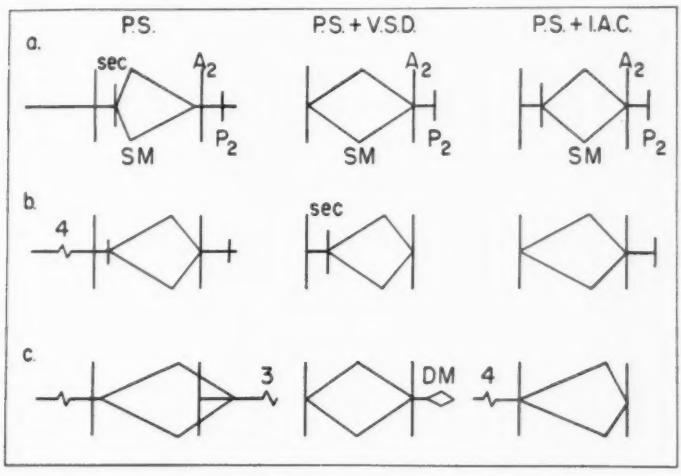

FIG. 8. Graphic representation of the phonocardiographic findings in pulmonary stenosis. (a) Mild. (b) Moderate. (c) Severe pulmonary stenosis.

tricular contraction, which causes blood to flow over the valve with great velocity. This increased velocity of flow produces the mid- and late systolic accentuation of the systolic murmur. With increasing increments of right ventricular hypertension, the murmur will be accentuated later in systole (figure 8). The fact that the time of accentuation of the systolic murmur changes after pulmonary valvulotomy seems to corroborate this explanation.

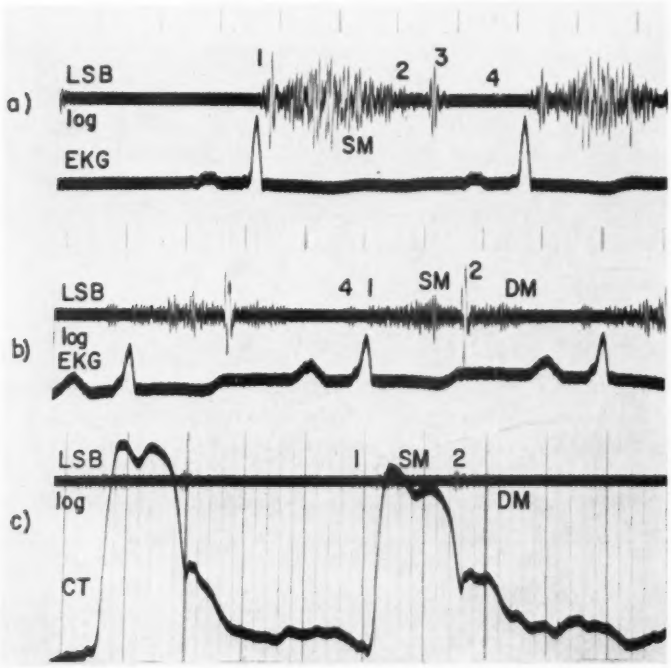

FIG. 9. Severe pulmonary valvular stenosis. RV pressure, 200/0 mm. Hg. PA pressure, 22/8 mm. Hg. (a) Before operation. Systolic ejection murmur with midsystolic accentuation. Third and fourth sounds. (b) One month after pulmonary valvulotomy. Note the remarkable change in the systolic murmur. An early diastolic murmur is present at LSB. (c) Two years after surgery. Very low amplitude systolic murmur. An early diastolic murmur is still present.

When the obstruction was relieved by operation, patients who had systolic murmurs with late systolic accentuation preoperatively showed early or midsystolic accentuation postoperatively (figure 9).

Using spectral phonocardiography, McKusick et al.[9, 10, 11] were able to distinguish three distinct characteristics in isolated pulmonary stenosis: first, a systolic murmur with "Christmas tree" appearance, with a late systolic peak; second, a unitary flat character of the second sound, loudest in the aortic area, due to aortic valve closure; third, a diminutive snaplike sound,

occurring 0.06 to 0.07 second after the aortic closure, due to pulmonic valve closure. They believed that this sound was produced when the pulmonary valve, reduced to a narrow membrane with central perforation, snapped when the right ventricular pressure decreased. This "pulmonary reversal snap" was compared to opening snap of the mitral valve in mitral stenosis.

In 1954 Reinhold and Nadas [12] pointed out that their data suggested an inverse relationship between the severity of pulmonary stenosis and the degree of the splitting of the second sound. This conclusion has not been proved by other investigators.[16, 22]

The systolic ejection click was first described by Potain [13] in 1900 as "claquement protosystolique." Wolferth and Margolies,[14, 15] Johnston [29] and, recently, Leatham [4, 16] attributed it to dilatation of the pulmonary artery in patients with pulmonary stenosis. Sound tracings simultaneous with pulmonary artery curves [4] showed that the systolic ejection click occurred about 0.03 second after the opening of the pulmonary valve. This suggested that this extra sound must be related to sudden distention of the pulmonary artery.

In patients with high right ventricular pressure and low pulmonary artery pressure, short isometric contraction must be expected, and this may be responsible for an early production of the systolic ejection click in cases with moderate or severe pulmonary stenosis.

An early pulmonary ejection sound was present in all patients with mild stenosis in Leatham and Weitzman's [16] series. However, even using simultaneous sound tracings at the apex and pulmonary area, we were unable to demonstrate such a high incidence. We recorded it in only 14 instances out of 56. In all of our cases it was associated with moderate poststenotic dilatation of the pulmonary artery. The relation of a systolic ejection click to the first sound in our series seemed to correlate well with the degree of right ventricular hypertension and with low pulmonary pressure. If the right ventricular pressure is moderately elevated, the click tends to be close to the mitral component of the first heart sound. We assumed that even in cases of severe stenosis it must be present, but we could not differentiate it from the vibrations of auriculoventricular valve closure.

The lack of dilatation of the pulmonary artery in cases of infundibular stenosis made it difficult to explain the presence of the ejection click in this condition. We recorded a systolic ejection click in one case of proved tetralogy of Fallot in which there was moderate dilatation of the aorta, and it is probable that the ejection click was aortic in origin.

It has been claimed by several authors [4, 22, 23, 30] that a differential diagnosis between tetralogy of Fallot and pulmonary stenosis with reversed shunt at atrial level can be made by phonocardiography. They stated that in tetralogy of Fallot the systolic murmur starts early in systole and stops at the aortic component of second sound. We attempted to differentiate these conditions in our study and were unable to demonstrate differential points.

In both situations the systolic murmur ended at the aortic component of the second sound in the majority of cases. The pulmonic component of the second sound was also absent in pulmonary stenosis with reversed shunt at atrial level, as well as in tetralogy of Fallot.

The type of stenosis, infundibular or valvular, did not determine a significant difference in the murmur. In three cases in our series of infundibular stenosis proved by necropsy, the murmur extended beyond the aortic component of the second sound, and a diminished pulmonic component was present. However, in eight cases of tetralogy of Fallot with infundibular stenosis the murmur stopped at the aortic component.

Kjelberg [17] pointed out that the second sound at the pulmonic area is the same in valvular and in infundibular stenosis. However, in infundibular stenosis, in his experience, the systolic murmur ended abruptly at the aortic component, whereas in valvular stenosis the murmur tended to extend through the aortic component. Several investigators [18, 19, 20, 21] have emphasized the difficulty or impossibility of distinguishing between valvular and infundibular stenosis, not only by auscultation but also by pressure tracings.

The absence of a pulmonary component of the second sound seemed to indicate severe stenosis. It was absent in 25 cases in the whole series (figure 1D).

The jugular venous pulse is very helpful in differentiating isolated pulmonary stenosis from cases of pulmonary stenosis with ventricular septal defect. In the great majority of cases in which we recorded giant or tall "a" waves, the ventricular septum was intact and the stenosis was moderate to severe (figure 4). In this condition the elevated right ventricular pressure produced a great resistance for the right auricle to overcome. This did not necessarily mean elevation of right auricular pressure, since it was normal in several cases in which the giant "a" waves were recorded. In all cases in which tall or giant "a" waves were recorded, a fourth heart sound was present.

A fourth sound, best recorded during inspiration, was much more frequent in cases of isolated pulmonary stenosis, supporting the concept, elsewhere discussed, that in pulmonary stenosis plus ventricular septal defect and right-to-left shunt the right auricle and right ventricle are under less stress than in isolated pulmonary stenosis. This sound is probably due to powerful atrial contraction in a right ventricle with high pressure, since we recorded it only in cases with moderate and severe stenosis. The presence of a fourth heart sound was an important diagnostic sign in differentiating pulmonary stenosis with intact ventricular septum from tetralogy of Fallot.

The determination of the work of the heart, as Starr [26] said, is one of the most important aspects in the estimation of the cardiac function: "It is a well recognized fact that the calculation of heart's work from cardiac output and mean blood pressure involves large errors. In order to obtain an accurate measure of the heart's work the flow at every moment must be multiplied by

the resistance at that moment and the cardiac ejection curve instant by instant is almost impossible to record." However, for clinical purposes the formula expressed before may be useful. As we demonstrate (figure 1A, B), the duration of right ventricular systole and the width of splitting of the second sound, which are good indexes of the severity of stenosis, kept a good correlation with the work of the right ventricle.

Summary and Conclusion

1. The auscultatory and phonocardiographic findings were studied in 56 patients with pulmonary stenosis proved by cardiac catheterization. These included 21 cases of isolated pulmonary stenosis, 30 cases of pulmonary stenosis associated with ventricular septal defect, and five cases of pulmonary stenosis with interatrial communication.

2. Isolated moderate and severe pulmonary stenosis usually produced a widely split second sound, with a diminished or absent pulmonic component, prolongation of right ventricular systole, and a systolic murmur going through the aortic component of the second sound. These findings correlated well with the degree of right ventricular hypertension.

3. If the systolic mumur showed late systolic accentuation, the right ventricular pressure was higher than 100 mm. Hg.

4. In cases of pulmonary stenosis with ventricular septal defect and right-to-left shunt (tetralogy of Fallot), the time of accentuation of the systolic murmur did not show a significant difference from the murmur of isolated pulmonary stenosis. In cases of tetralogy of Fallot, the murmur usually stopped at the aortic component of the second sound. However, in five cases of proved tetralogy of Fallot, the murmur went through the aortic component of the second sound.

5. The pulmonic component of the second sound was recorded in three cases of proved (surgery and post mortem) tetralogy of Fallot.

6. The presence of third and fourth sounds indicated marked elevation of the right ventricular pressure.

7. The presence of giant "a" waves in the venous tracing suggested a diagnosis of moderate to severe pulmonary stenosis with intact ventricular septum.

8. The presence of a systolic ejection click was helpful in the evaluation of the degree of stenosis, but it was recorded only 14 times in the whole series, and it was present in only mild and moderate stenosis.

9. A mid-diastolic rumble was recorded in four cases of tetralogy of Fallot but in none of the cases of isolated pulmonary stenosis.

10. The right ventricular work was increased in cases of moderate and severe pulmonary stenosis. In such situations the duration of right ventricular systole was prolonged.

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SUMMARIO IN INTERLINGUA

Esseva studiate le constatationes auscultatori e phonocardiographic in 56 patientes con stenosis pulmonar que habeva essite demonstrate per catheterismo cardiac. Le series includeva 21 casos de isolate stenosis pulmonar, 30 casos de stenosis pulmonar associate con defecto ventriculo-septal, e cinque casos de stenosis pulmonar con communication interatrial.

Isolate stenosis pulmonar de grados moderate o sever produceva usualmente un largemente findite secunde sono, con reduction o absentia del componente pulmonic, prolongation del systole dextero-ventricular, e un murmure systolic transversante le componente aortic del secunde sono. Iste constatationes esseva ben correlationate con le grado del hypertension dextero-ventricular. Quando le murmure systolic exhibiva accentuation tarde in le systole, le tension dextero-ventricular esseva superior a 100 mm de Hg.

In casos de stenosis pulmonar con defecto ventriculo-septal e shunting dextero-sinistre (tetralogia de Fallot), le tempore del accentuation del murmure systolic revelava nulle significative differentia in comparation con le murmure de isolate stenosis pulmonar. In casos de tetralogia de Fallot, le murmure cessava usualmente al componente aortic del secunde sono. Tamen, in cinque casos de clarmente establite tetralogia de Fallot, le murmure transversava le componente aortic del secundo sono. Le componente pulmonic del secunde sono esseva registrate in tres chirurgicamente o necropticamente demonstrate casos de tetralogia de Fallot.

Le presentia de un tertie e quarte sono indicava marcate elevationes del tension dextero-ventricular.

Le presentia de gigante undas "a" in le registration venose suggereva le diagnose de moderate o sever stenosis pulmonar con intacte septo ventricular.

Le presentia de un clic de ejection systolic esseva de adjuta in le evalutation del grado del stenosis, sed illo esseva registrate solmente 14 vices in le serie complete, e illo esseva presente solmente in casos leve o moderate de stenosis.

Un rolamento medie-diastolic esseva registrate in quatro casos de tetralogia de Fallot sed in nulle del casos de isolate stenosis pulmonar.

Le labor dextero-ventricular esseva augmentate in casos de moderate e sever stenosis pulmonar. In tal situationes le duration del systole dextero-ventricular esseva prolongate.

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THE EFFECT OF CHILDBEARING ON THE COURSE OF RHEUMATIC HEART DISEASE: A 25-YEAR STUDY * †

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The immediate prognosis for women with rheumatic heart disease during pregnancy and in the puerperium is fairly well known, and valid criteria have been established for the management of these patients. On the other hand, the ultimate effect of childbearing on the course of rheumatic heart disease is not so well known. The present study was undertaken in an attempt to shed further light on this problem. This report deals with a large group of patients carefully studied by the same group of physicians, together with a report of the follow-up findings for those same patients at the end of a 25-year period.

The records on which this study is based number 455, and, as a result of an intensive follow-up, the fate of 97.4% of the entire group was determined. Such a study seemed bound to shed some light on this problem. Indeed, a preliminary report was presented in 1954.‡ However, critical analysis of the statistical material revealed biases which were not recognized at the beginning. Because of these biases, we were not inclined to publish our results. However, an analysis of such a large group of patients followed over a 25-year period is very unusual, and it should be available to others working in this field. We feel that not only are the clinical impressions obtained worth while, but also that a description of the difficulties encountered in our statistical analyses may help other investigators in clinical studies. It is not well known to most clinicians that there are natural biases in this type of study which are apparently impossible to eliminate. We therefore decided to publish our results.

Method

To obtain a large number of cases followed over a long period, it was decided to analyze the records of all female patients with rheumatic heart disease treated in the adult cardiac clinic of The Brooklyn Hospital from

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its inception in 1924 through the year 1948. This clinic is affiliated with the New York Heart Association, and has used the detailed record forms and the diagnostic criteria established by that organization from its beginning. In addition, the senior author was chief of the clinic through the entire period, thus assuring that standards of care did not change.

In the year 1948 an intensive follow-up of all closed cases was begun. Whenever possible, the patients were brought back to the clinic for re-examination. This included an interval history, physical examination, and x-ray of the heart with fluoroscopy. In addition, the records of all active cases were reviewed for completeness and brought up to date.

The present study therefore includes the records of all females with rheumatic heart disease treated in the 25 years from 1924 through 1948 except (1) records which were too incomplete for a diagnosis of heart disease, or which could not be completed because neither the patients nor supplementary medical records pertaining to their cardiac disease could be located; (2) records of patients who died before the childbearing age, arbitrarily set at 19 years unless they became pregnant before that age; (3) records of patients without a history of rheumatic infection in whom heart disease was discovered after the childbearing period. With these exclusions, the records on which this study is based number 455.

All the "closed" or inactive patients were followed, and all subsequent available records pertaining to their disease obtained. This required the full time of two trained investigators and meant searching for records in hospitals and health departments throughout New York City and the rest of the country. The fate of these patients—at least whether they were dead or alive—was known up to the year 1948 or later in 433 (97.4%) of the entire group.

The patients whose records were so studied were separated into those who were parous and those who were not parous at the time of their first observation. Both of these groups were further divided into those who did and those who did not become parous after first observation. This method permitted examination of the four groups as to their comparability at the first observation, particularly as to severity of the disease, in addition to the results of the follow-up. The four groups were then analyzed as to the type of manifestations of infection, number of recurrences, age, duration of infection, type of valvular lesion, presence or absence of atrial fibrillation, occurrence of failure, effect of multiparity, and functional classification.

Problems in Statistical Evaluation

The greatest difficulty in determining the effect of childbearing on the course of rheumatic heart disease has been the securing of a satisfactory control series. Some investigators have used males with rheumatic heart disease, but this is open to the objection that the course may be different in the two sexes. Others have used nulliparous females. The possibility that

these women did not have children because their heart disease was too severe to make it advisable is a very real one and is suggested by this study. All data tend to illustrate that the selective effect of the very factor we are studying makes the use of controls practically impossible. Miller and Metcalfe [1] have recently pointed out again that two thirds of the mortality from rheumatic heart disease occurs before the age of puberty. Mere survival to the childbearing age is a selective factor. Bunim and Appel [2] called attention to the fact that childbearing occurs at a period in the life cycle when rheumatic heart disease is relatively inactive. Hamilton [3] discussed several factors which may have a naturally selective effect on whether

TABLE 1

Per Cent Mortality in the 10 Years Following First Observation Related to Age and Parity at First Observation

Age at First Observation	Parity at First Observation				
	0	1	2	3+	Total
15–19	13.9 (38)	— (6)	— (0)	— (0)	21.4 (44)
20–24	23.1 (31)	13.3 (42)	— (10)	— (3)	19.9 (86)
25–29	54.6 (16)	20.4 (32)	6.8 (16)	8.3 (12)	22.6 (76)
	0–1				
30–34	40.6 (13)		26.8 (19)	33.7 (25)	32.9 (57)
35–44	53.7 (23)		54.2 (15)	49.5 (32)	51.9 (70)
Total	29.4 (103)	24.5 (98)	28.9 (60)	35.4 (72)	29.3 (333)

patients become pregnant. He points out that patients may avoid or leave clinics where therapeutic abortions are not performed. Mortality rates are much higher among unmarried women in the general population, probably because the handicapped are less likely to marry.

Not only do the above factors influence mortality, but also more recently, treatment has materially affected prognosis. Hamilton and Thomson [4] reported a drop in maternal mortality from 15% in 1921 to an average of 3% for the subsequent 12 years. In our series of 317 parous cases, nine died during pregnancy or at time of delivery, a mortality rate of 2.83% for a 24-year period. However, no patient died in the last five years of the study. It is the impression of many clinicians that rheumatic fever has become less virulent in its manifestations in recent years. The number of deaths during pregnancy and the puerperium is so small in relation to the

mortality of the general population as to render all data statistically not significant.

In addition to these more general reasons for bias, the selective effect of the factors we are studying becomes even more obvious when statistical analysis is attempted. To illustrate these problems more specifically, the two tables for mortality are presented first, together with explanatory notes. The other tables presenting the various facets of our study are also subject to the same criticisms.

In table 1, to obtain greater homogeneity, the data were restricted to white females who were between the ages of 15 and 44 years at first observation. The life table method was used to estimate the per cent

TABLE 2

Per Cent Mortality in the Interval Between Five and 15 Years After First Observation Related to Children Born in the Five Years After First Observation

Interval in Which Mortality is Measured	Children Born in the Five Years After First Observation	Parity of Patient at First Observation		
		0	1	2+
5–9 years after first observation	None	16.9 (44)	19.8 (37)	11.7 (36)
	One or more	3.9 (27)	3.5 (31)	9.3 (33)
10–14 years after first observation	None	23.6 (31)	20.3 (24)	33.3 (26)
	One or more	13.7 (24)	14.3 (24)	23.9 (28)
5–14 years after first observation	None	36.5 (44)	36.1 (37)	41.1 (36)
	One or more	17.1 (27)	17.3 (31)	31.0 (33)

mortality in each group. This method makes an allowance for those who were not followed for the full 10 years of observation. Those who died in the first five-year period cannot be included in the second period. It will be noted that mortality increases markedly with age.

There is little change in mortality when women of different parity are compared (bottom row of the table). However, it is also apparent that women who are nonparous, or of low parity, tend to be younger than those who have had two or three children. On this account they would not only be expected to have lower mortalities, but would also have more opportunity to have more children. *At a given age,* mortality is much higher for nonparous than for parous women, and decreases with increasing parity. This becomes apparent if the body of the table is examined, reading horizontally along the rows. The relationship of mortality with age exists at each

parity. In fact, this relationship with age is more apparent when parity is held constant than in the total of all parities. These facts appear when one reads vertically down the columns of the body of the table. Thus this table shows that both age at first observation and parity *at a given age* are markedly related to mortality.

Table 2 attempts to answer the question, "How does mortality differ for women who do and do not have children in the first five years after first observation?"

Since table 1 has shown that both parity and age at first observation are markedly related to mortality, it is necessary to restrict the groups examined for both parity and age. To allow for parity, patients who were nonparous, and those who were para 1 and para 2 were examined separately. To allow for age, the observations in each of these parities were restricted to limited age groups. In the examination of nonparous and the para 1, only women between the ages of 15 and 29 were included. In the examination of para 2, only women between 20 and 34 years of age were included.

Further precautions are also necessary. These additional precautions are taken because the probability of having children in the five years after first observation is related to the probability of death in that period. For example, a woman dying within two years of first observation is less likely to have had a baby than one who survives the whole five years. Therefore, the group of women who had no children during the first five years after observation is likely to be biased in the direction of a higher death rate. To decrease this bias, the examination has been restricted to women who survive the first five years of observation. The mortality has been measured only in the two periods, five to nine years after first observation, and 10 to 14 years after first observation. The bottom row shows summary figures for the total mortality in the period five to 14 years after the first observation, and omits the first five years because of this natural bias.

A study of the 85 patients who were nonparous and aged 15 to 29 years at the time of first observation demonstrates the relationship of parity to mortality. Of these 85 nonparous patients, 12 died and two were lost trace of in the first five subsequent years, leaving 71 patients alive and traced five years after first observation. Of these 71 patients, 27 had had one or more children during the first five years after first observation, while 44 remained nonparous. The mortality of the 27 women who became parous was 3.9%, while the mortality of those 44 women who remained nonparous was 16.9%.

At the end of 10 years after the first observation, 31 of the 44 parous women were still alive, and 24 of the 27 women who had become parous were still alive. The mortality among the nonparous women was 29.3%, and for those who became parous it was 11.1% during the second five years after first observation.

Before the end of the fifteenth year after first observation an additional 23.6% of the nonparous and 13.7% of those who became parous had died.

It will be seen that in all parity groups the mortality is considerably higher for women who had no children after first observation than for women who had one or more children.

In summary, these two tables show that (1) women who were nonparous at first observation had a poorer survival rate than did the parous, and the most favorable survival rates were exhibited by women who had had two or more full term pregnancies prior to first observation; and (2) women who had subsequent children within five years after the first observation had much better survival rates than did women who did not become pregnant after first observation.

The possibility that pregnancy in itself exerts a beneficial effect on the course of rheumatic heart disease cannot be ruled out or investigated on these data. There is certainly no evidence that pregnancy has a detrimental effect. The suggestion is, however, that the nonparous are less healthy than are the parous, and the more favorable experience of the parous women probably results from a tendency of the nonparous not to become pregnant.

Factors Other Than Mortality

The opinion among the earlier workers in this field was almost unanimous that pregnancy caused deterioration in the cardiac status, and it was usual to advise women with mitral stenosis not to marry. In 1906 French and Hicks [5] pointed out that the few studies on which this opinion was based involved only women already in serious cardiac difficulties. Those who had gone through pregnancy without trouble were omitted from the analyses. In 1933 Gilchrist and Murray-Lyon,[6] in a small group of cases studied at post mortem, were unable to show any difference in duration of disease or age at death in parous or nulliparous women with rheumatic heart disease. In 1944 Boyer and Nadas [7] studied a small group of cases from which they excluded all those who died before age 40 so as to overcome the objection that many nulliparous women have more serious heart disease and should not be used as controls. They found that there was no significant difference in the age at death of patients who were 40 years of age or older among nulliparous women, parous women after four or more pregnancies, and males. In 1951 Jones [8] studied 74 cases and concluded that there was no evidence that in the majority of cases pregnancy leads to more than temporary deterioration in the cardiac condition, or that repeated pregnancies appreciably shorten life.

Although our study involves an unusually large group, attempts at analysis break the group into so many subdivisions that the numbers become small for any one section. However, we could find no consistent differences between the parous and nonparous groups with respect to age at first infection, number of episodes of infection prior to first observation, valvular lesion at first observation, or nature of the recorded infection. This failure

to show such consistent differences corresponds to the findings of many other workers in this field.

There do seem to be differences with respect to functional classification at the first observation. This is particularly true when comparing women of different parity at the first observation. For all age groups that can be examined, the percentage in functional classification 1 is higher in the parous than in the nonparous. The trend is not so regular when one compares the women who became parous after the first observation with those who did not. Even here, however, there is a definite trend toward a higher percentage of group 1 classifications than among those who became pregnant after the first observation. Again the suggestion is that the nonparous were less healthy than were the parous. Certainly any implication that the two groups were similar and that the difference between them in mortality experience was related to pregnancy could not be upheld.

In this study, functional classification seemed to be the most valuable guide as to prognosis in the individual case, and a suggestive factor as to long-term prognosis and the effect of pregnancy on rheumatic heart disease. However, this possible significance applied only to group 1 classification. This factor may also be misleading, for when classifications 2, 3 and 4 were considered, the correlation did not apply.

Probably the difference could be due to our present method of classification. It is obvious that the patient who is in class 2 or 3 without treatment has not the same status as does the patient who remains in those groups only while she is maintained on digitalis, low sodium diet and diuretics. Nor is the patient who is in class 2 or 3 while she is pregnant necessarily in the same class before or after pregnancy. When patients are considered in groups, functional classification loses its value progressively as the patient's condition has deteriorated to the status in groups 2, 3 and 4. Group 1 patients are by definition a group with a more favorable prognosis.

Summary

A report is presented of 455 cases of rheumatic heart disease in women of the childbearing age group, together with a report of a 25-year follow-up. These cases were analyzed as to parity, nonparity, mortality, and the factors usually considered to be significant from a prognostic point of view, in order to answer the simple question, Does pregnancy affect the long-term prognosis in rheumatic heart disease?

It is pointed out that the selective effect of the very factor we are attempting to study creates a natural bias which precludes such data from providing an answer to the question we are studying. Therefore, this type of study cannot give us more than a clinical impression. The possibility that pregnancy in itself exerts a beneficial effect cannot be ruled out or investigated by these data. We can state that the more favorable experience of the parous woman probably results from a tendency of the nonparous not

to become pregnant. However, there is certainly no evidence that pregnancy has a long-term detrimental effect in a large group.

Individually, pregnancy must be looked upon as a temporary hurdle, and each case must be considered individually. Undoubtedly pregnancy does in some individuals provoke or hasten invalidism and shorten life, as well as cause death, as Hamilton [8] has pointed out. The incidence of cardiac failure and death is much higher during an individual year containing a pregnancy than in another comparable year in that same person's life. As he states, treatment markedly influences the over-all mortality, but only in "favorable" groups. In his experience, the mortality in the "unfavorable" groups is not greatly changed. Therefore, it is still the doctor's duty to weigh the relative risks of pregnancy in the presence of rheumatic heart disease, especially in the "unfavorable" cases early in pregnancy. A patient's death may not be statistically significant, but it can still be a great personal tragedy. In some cases, fortunately now very rare, therapeutic abortion may still be indicated.

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SUMMARIO IN INTERLINGUA

Le ultime effecto de repetite pregnantias super le curso de rheumatic morbo cardiac non es ben cognoscite. Occurre il un augmento de morbiditate e del mortalitate? In le effortio de responder a iste questiones, analyses esseva effectuate del dossiers de 455 feminas de etate ovulante con rheumatic morbo cardiac tractate in le curso del periodo de 25 annos inter 1924 e 1949 al clinica cardiac del Hospital Brooklyn. Gratias a un intense programma de recercas, le destino de 97,4% del gruppo total esseva determinate. Le cifras de mortalitate esseva establite e analysate in correlation con le rango de nulli-, uni-, o pluriparitate del feminas e etiam con altere factores que es usualmente considerate como significative ab le puncto de vista prognostic.

Le analyse de nostre datos monstra que (1) le feminas qui esseva nullipare al tempore del prime visita al clinica cardiac habeva cifras de mortalitate minus favorabile que le feminas qui esseva uni- o pluripare a ille tempore, durante que le plus favorabile cifras de mortalitate esseva constatate in le gruppo de feminas qui habeva completate duo pregnantias o plus ante le tempore de lor prime visita al clinica e (2) le feminas qui parturiva infantes intra cinque annos post lor prime visita al clinica habeva multo plus favorabile cifras de mortalitate que le feminas qui non deveniva pregnante post le tempore de lor prime visita.

Es signalate que le factor mesme que nos desira studiar exerce un effecto selective super le datos que assi deveni prejudiciate. Per consequente le datos es incapace a responder al question que nos investiga, e iste typo de studio pote resultar solmente in un impression clinic. Le possibilitate que le pregnantia per se exerce un effecto benefic non pote esser rejicite, sed il es etiam ver que illo non pote esser verificate per medio de nostre datos. In omne caso, le datos offere nulle prova que le pregnantia ha un effecto nocive a longe vista in large gruppos de subjectos.

Ab le puncto de vista del femina individual, le occurrentia del pregnantia debe esser considerate como un periculo temporari, e omne caso individual debe esser tractate individualmente. Sin dubita, in casos individual le occurrentia de un pregnantia pote provocar invaliditate o accelerar lo; illo etiam pote accurtar le vita e mesmo causar le morte, como Hamilton lo ha signalate. Le incidentia de disfallimento cardiac e de morte es multo plus alte in annos con pregnantias que in altere comparabile annos. Hamilton ha etiam ration in su assertion que le tractamento medical exerce un marcate influentia super le mortalitate general, sed isto vale solmente pro le gruppo "favorabile." In su experientia, le mortalitate in le gruppo "disfavorabile" non es grandemente influentiate per le tractamento. Assi il remane le deber del medico ponderar le riscos relative de pregnantia in patientes con rheumatic morbo cardiac, specialmente in casos "disfavorabile," le plus precocemente possibile in le curso del pregnantia. Il es ver, le morte de un patiente individual non es statisticamente significative, sed nonobstante illo pote esser un grande tragedia personal. In certe casos—que es felicemente multo rar in nostre dies—un abortion therapeutic es possibilemente indicate.

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MANUAL COMPRESSION OF THE CAROTID VESSELS, CAROTID SINUS HYPERSENSITIVITY AND CAROTID ARTERY OCCLUSIONS *

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In recent years various discussions of cerebral vascular disease have emphasized the importance of the vessels in the neck. Much of this literature has been devoted particularly to the patency of the common and internal carotid arteries, and to the technic of arteriography, which has allowed adequate investigation of these vessels. Another means of studying the cerebral circulation—manual compression of the carotid arteries—has received somewhat less comment.

That compression of a carotid artery may induce a change in cerebral function was apparently known by the ancient Greeks. The term "carotid" is said to have been derived from the Greek word *kápos,* meaning deep sleep.[1-4] The means by which deep sleep or syncope or seizures can be produced by manipulation of the carotid arteries are not altogether clear. At least two possible mechanisms are known: (1) the result of carotid sinus hypersensitivity, and (2) a cerebrovascular ischemic effect, most commonly found with an occlusion of the contralateral carotid artery. The purposes of this communication are: (a) to present a technic for carotid compression which has been found to be a valuable addition to the routine neurologic examination; (b) to review briefly the clinical features of carotid sinus hypersensitivity and carotid artery occlusion, and (c) to distinguish between the results obtained by manual compression of the carotid artery with carotid occlusive disease and those obtained with carotid sinus hypersensitivity.

Technic of Carotid Compression

The recommended technic for manual compression of the carotid artery is shown in figure 1. Whenever possible, the test is performed with the patient in the sitting position. The examiner stands behind or in front of the patient, and places the fingers of his right hand as low on the neck as he can clearly feel carotid pulsations. By placing the fingers medially to the sternocleidomastoid muscle, and by reaching under it if necessary, he can feel the carotid pulsations fairly low in the neck in most patients. Palpation

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of the pulse may be facilitated by extension of the neck. The right hand is used to occlude the right carotid, and later the left hand for the left carotid. The fingers of the other hand are placed over the ipsilateral superficial temporal pulsations just in front of the ear. Pressure is then exerted as firmly as possible with the compressing hand, and the artery is pressed against the transverse processes of the adjacent vertebrae. The adequacy of such compression of the common carotid artery is readily confirmed by noting the loss of the superficial temporal pulse with the other hand. Since utilization

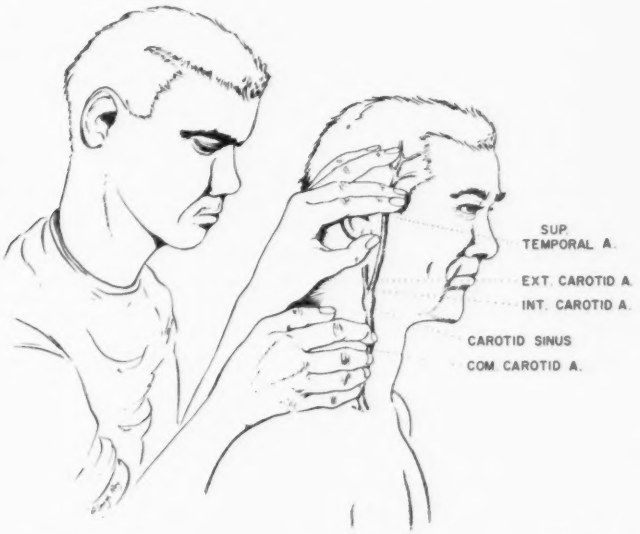

FIG. 1. Technic for carotid compression. Although the examiner is shown behind the patient, additional information may be obtained from the test by standing in front of the patient and observing his eye movements.

of this "superficial temporal control" technic (which has been employed previously for other purposes [5]), it has been possible to obtain consistent, reproducible results with repeated carotid compression.

The compression is maintained for 30 seconds unless the patient loses consciousness or has a seizure, at which time the compression is immediately discontinued. Other symptoms, such as paresthesias or dizziness, are not considered to be diagnostic, and are not indications for interrupting the procedure. If syncope or seizures are produced, the test is repeated while an assistant watches pulse rate and blood pressure changes. If there is a suspicion or evidence of carotid sinus hypersensitivity, the compression is repeated after atropine, a vasopressor or procaine has been administered (as will be described below).

Personal Observations

Manual compression of the carotid arteries was performed in 40 patients with occlusive disease of their contralateral carotids. These occlusions were proved in all patients by arteriography, surgery or autopsy. It was possible to produce syncope and/or seizures in 26 of the patients tested by this maneuver. Convulsive movements were produced slightly more often than was loss of consciousness. The great majority of patients with carotid occlusions, however, showed both seizures and syncope when their patent carotids were compressed. The seizures involved predominantly the arm and leg contralateral to the side of compression, although ipsilateral and generalized seizures were also produced. Further details can be found elsewhere [6] concerning these clinical results, as well as some of the electroencephalographic changes produced by carotid compression in patients with carotid occlusive disease.

Carotid compression tests have also been performed on the Medical and Surgical Wards of this hospital in 265 unselected patients who were considered to be free from detectable cerebral disease by their physicians. Eleven patients from this "control" group exhibited syncope and/or seizures when their carotids were compressed. Ten of these patients were over the age of 50. Special studies to exclude possibly asymptomatic carotid occlusions were not performed.

Carotid compression studies have been employed in almost all admissions to the Neurological Service of the Mount Sinai Hospital during the last four years. Many patients with brain disease not due to carotid occlusions have exhibited syncope and/or seizures in response to the initial test. A tendency has been noted, however, for subsequent carotid compression to be without effect in these patients. This is in contrast to the results obtained in patients with occlusive cerebrovascular disease, in whom the results of the test are generally reproducible. Recently, we have been interested in observing the eye movements of patients who exhibit "positive" (i.e., syncopal or seizure) responses to carotid compression. On several occasions, vertical nystagmus has been noted just prior to the onset of syncope or seizure. The exact significance of this is unclear at present, but it may represent possible basilar artery insufficiency during the period of carotid compression.

Carotid Sinus Hypersensitivity

Little has been added to the description of carotid sinus hypersensitivity since these attacks were popularized over 20 years ago by Soma Weiss and his colleagues.[7-9] The classic syndrome of a hypersensitive carotid sinus consists of sudden episodes of syncope, which can occur spontaneously or can be reproduced by manipulation of the carotid sinus. The attacks of syncope, which usually last a matter of seconds, may be preceded by such

aurae as blurred vision, oscillopsia, tinnitus, scotomata, vertigo, paresthesias and hallucinations.[3] Seizure phenomena not uncommonly accompany the attack. These may be focal or generalized,[10] and may occur without loss of consciousness.[8] These episodes may be distinguished from seizures of other etiology by their occurrence predominantly when the patient is in the vertical position, by their rapid onset and short duration, by the usually clear postictal sensorium, and by their induction by carotid sinus pressure.[11] It may also be possible to elicit a history of carotid sinus stimulation (e.g., wearing a tight collar, turning the head, etc.) prior to the onset of "spontaneous" attacks.[12, 13]

It has been customary to classify the mechanisms by which carotid sinus hypersensitivity is manifested into three types: (1) the vagal or cardioinhibitory reflex, which is characterized by a sharp drop in pulse rate or asystole, and is abolished by atropinization; (2) the depressor or vasomotor reflex, which is characterized by a fall in blood pressure, and is prevented by epinephrine; and (3) the "cerebral" reflex, which occurs without appreciable pulse rate or blood pressure changes, and is abolished neither by atropine nor by epinephrine. This classification has never been challenged until recently, after further studies on the functions of the carotid arteries. For several years now, comments have appeared in the literature indicating that many patients with the "cerebral" form of carotid sinus hypersensitivity may actually have been suffering from occlusive cerebrovascular disease, and that the symptoms produced by carotid pressure in such patients may have been purely ischemic effects.[14, 15] Gurdjian et al. have recently published their belief that this so-called "cerebral" form of carotid sinus sensitivity is completely nonexistent.[16]

While it is true that most patients previously considered to have the "third" type of carotid sinus sensitivity were actually victims of cerebrovascular insufficiency, a form of carotid sinus hypersensitivity unassociated with detectable changes in pulse rate or blood pressure would still appear to exist, although occurring quite infrequently. That this is so is suggested by the reports of patients in whom such sensitivity was abolished by procaine infiltration of the sinus area [17] by surgery [17-19] or by radiotherapy.[20] Furthermore, symptoms did not occur in some of these patients with manual compression of the carotid below the region of the sinus, but did when compression was applied at the level of the sinus.[8, 21] These observations and others recently summarized by Engel [54] cannot be explained on a purely ischemic basis. However, in view of the now recognized great frequency of occlusive disease of the carotid arteries, the present rarity of the "cerebral" form of carotid sinus hypersensitivity, and the similarity of the responses obtained by carotid compression in both conditions, occlusive vascular disease would certainly seem to have been the correct diagnosis in many patients thought to have the latter condition.

Carotid Artery Occlusion

With the current extensive utilization of carotid angiography, occlusions of the carotid arteries have come to be well recognized as a cause for neurologic deficit. In a recent angiographic study of 200 patients who presented with acute "strokes," over 20% were found to have carotid occlusions.[22] Patients with such occlusions may present very varying symptomatology.[23-26] Thus, clinical pictures of expanding mass lesions or of middle cerebral artery occlusions are well known. Intermittent symptoms of cerebral dysfunction, visual symptoms or no symptoms at all can occur. The diagnosis of carotid occlusion may be suggested by any of the following features, all of which occur quite rarely in actual practice:[26] transient monocular blindness[27] or optic atrophy[20] with contralateral hemiparesis; ipsilateral Horner's syndrome;[29] dilatation of the superficial vessels of the face;[30] diminished carotid pulsations,[31] and a cranial[32] or carotid bruit.[33] On the other hand, there are two extremely useful clinical diagnostic maneuvers for carotid occlusion. These are (1) measurement and comparison of the pressures of the retinal arteries (ophthalmodynamometry), which gives diagnostic values in over 70% of patients with carotid occlusions,[34-36] and (2) manual compression of the contralateral carotid, which will be discussed further.

Patients with carotid occlusions may show several signs and symptoms when their patent carotid is compressed. Thus, there may be syncope and/or seizures,[4, 6, 37-41] contralateral paresthesias and hemiparesis,[42, 43] and electroencephalographic abnormalities.[5, 41, 44-46] Narrowing of the retinal arteries (observed at funduscopy)[42] and changes in the retinal artery pressures[30] have also been reported. In our experience, the production of syncope or seizures by manual compression of the carotid artery is the most frequent finding in patients with contralateral carotid occlusions. These responses were recently reported by others[47] to occur in 44 of 52 patients so tested. It has been possible to correlate such responses directly with collateral circulation via the compressed carotid. Those patients with carotid occlusions who do not exhibit syncope or seizures when their patent carotid is compressed are almost always *not* receiving collateral circulation from *that* carotid.[6]

Patients who exhibit syncope or seizures with carotid compression, however, are not necessarily victims of occlusive disease of their contralateral carotids. Such responses, not due to carotid sinus sensitivity, may occur in patients with anterior cerebral artery occlusions,[39, 40, 48] basilar artery insufficiency,[39-41, 47] increased intracranial pressure[40, 47] and in other conditions.[6, 40, 41, 44] Therefore, the production of seizures or syncope with carotid compression can not be considered to be absolutely diagnostic for a contralateral carotid occlusion.

Differentiation Between Carotid Sinus Hypersensitivity and Ischemic Responses Due to Occlusive Cerebrovascular Disease with Carotid Compression

Although the syncope and/or seizures which occur with carotid sinus hypersensitivity may be quite similar to those produced by carotid compression with contralateral carotid occlusions, it is possible to distinguish between the two types of effects in almost all patients. If the compression is applied low in the neck, away from the carotid sinus (figure 1), the effects of carotid sinus hypersensitivity can usually be minimized or excluded. It is said that a rare patient may show sinus sensitivity following release of the compression,[8] but this has yet to be observed in the authors' experience. Even in obese patients with short necks, in whom it may be necessary to compress

Table 1

Usual Distinguishing Features of Carotid Sinus Hypersensitivity and Ischemic Response Produced by Carotid Compression

	Carotid Sinus Sensitivity			Ischemic Response
	"Vagal" Type	"Depressor" Type	"Cerebral" Type	
Asystole or significant slowing of pulse	+	—	—	—
Significant drop in blood pressure	—	+	—	—
Onset following compression	Immediate	Immediate	?	After several seconds' delay
Positive response to compression below sinus	—	—	—	+
Reproducibility of response following atropine	—	+	+	+
Reproducibility of response following vasopressors	+	—	+	+
Reproducibility of response following procainization of sinus	—	—	—	+

close to the location of the sinus, the two types of responses may still be differentiated. As a general rule, the onset of syncope or seizures with carotid sinus sensitivity is within two to three seconds; the ischemic effects in the brain may take several more seconds to appear. Moreover, the pressure necessary to induce an effect of a hypersensitive carotid sinus is much less than that required for cerebral vascular ischemia. The vagal and depressor types of carotid sinus sensitivity may be suspected by the appropriate pulse rate and blood pressure changes, and can usually be excluded by repeating the test after administering 0.4 mg. atropine intravenously (for the vagal type), or a suitable vasopressor intramuscularly (for the depressor type). If there is still a doubt as to the type of response occurring, the test can be repeated following infiltration of the area around the sinus with from 5 to 8 c.c. of 1% procaine. This chemical denervation

of the sinus, if properly performed, may exclude all three types of carotid sinus hypersensitivity, but it leaves the ischemic response unaltered.

Table 1 summarizes the means of distinguishing the three types of carotid sinus sensitivity from each other, and from the ischemic response noted with contralateral carotid occlusion.

Complications from Carotid Compression

Carotid manipulations have frequently been considered to be too dangerous for routine performance.[49, 50] In 1947 Zeman and Siegel collected nine reported cases of hemiplegia possibly related to carotid sinus manipulation, and added one of their own.[51] The patient reported by Brannon [52] the following year had actually sustained a severe neck injury, and cannot be included among the complications from the procedure. A patient with temporary aphasia and monoplegia following carotid compression was cited in 1954.[53]

While complications may follow carotid compression, their occurrence would appear to be quite infrequent. Of the several hundred patients whose carotids were compressed by Webster and Gurdjian, only two experienced significant complications.[40] In over 20 years of active practice of one of the authors (M. B. B.), during which time several thousand carotids have been compressed, only two untoward reactions have occurred. In his experience with manipulation of the carotid sinuses of well over another thousand patients, Sigler reported no permanent complications.[10] In the last four years, carotid compression studies have been performed on almost all patients admitted to the Neurological Service of The Mount Sinai Hospital. There has been only one probable complication (increased persistent neurologic deficit) from the procedure during this period of time.

These complications, though rare, may seem to indicate that there is an inherent danger from carotid compression. It is the present feeling of the authors, however, that the information to be gained from careful performance of the procedure far outweighs the possible risks.

Summary

A technic is presented for manual compression of the carotid artery (with superficial temporal artery control). This procedure may be of aid in recognizing occlusive disease of the contralateral carotid. Some of the clinical features of carotid occlusion and carotid sinus hypersensitivity are reviewed, and the means of distinguishing between the responses obtained by carotid compression with each condition are described.

Summario in Interlingua

Ha essite trovate que le compression manual de un arteria carotide in le parte inferior del collo es un importante addition al routine del examine neurologic. Le

technica del manovra debe includer le palpation del pulso in le arteria temporal superficial como medio pro verificar le adequatia del compression.

Compression carotide produceva definite signos de ischemia cerebral (syncope e/o convulsiones) in 26 ex 40 patientes con verificate occlusiones carotide contralateral. Simile responsas esseva evocate in 11 ex 265 non-seligite patientes sin morbo cerebral. Tamen, iste effectos esseva etiam obtenite in multe patientes con morbo cerebral non causate per occlusiones carotide.

Le effectos ischemic de compression carotide pote esser differentiate ab le effectos reflexe de hypersensibilitate del sino carotide per le facto que illos occurre solmente post plure secundas de retardo e que illos pote esser reproducite quando le compression es applicate ben infra le sino carotide. Usualmente nulle significative alterationes del rapiditate del pulso e del tension de sanguine occurre in association con iste responsas ischemic. In plus, ni le administration intravenose de atropina, ni le uso de un vasopressor intramuscular o de novocaina pote abolir le signos ischemic effectuate per compression carotide. Ben que in rar casos il es possibile que complicationes resulta del compression carotide, le manovra pare esser de adjuta in le recognition de occlusiones carotide contralateral e de altere formas de insufficientia cerebro-vascular.

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THE STATUS OF TRANQUILIZING DRUGS—1959 *

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DRUGS to give man a sense of peace or emotional comfort have been used since time immemorial, and have included everything from alcohol, opiates and the solanaceous group through marihuana, bromides, barbiturates and, more recently, a new group of drugs which we include under the general terms "tranquilizers," or ataractics.

Just how did this come about? What was man seeking? Why did he have to avoid certain unpleasant sensory experiences, signals that came into his eyes, ears, nose, tactile system, taste, or combinations thereof? What was going on within his brain that he was seeking a respite even in the earliest days? Was it fear of the dark, attack by animals, by fellow man? Was he frightened by the phenomena of nature—thunder, lightning, torrential rains, freezing cold, avalanches, landslides or the like?

Within him were defenses against anxiety, the same mechanisms we all possess to handle tension. We teach this in our earliest classes in psychophysiology and psychopathology in the Medical School, just as we teach the defense mechanisms against infection, or physical stresses, like cold or heat. This is normal human physiology, which enables a soldier to go into combat despite fear, which permits an individual to go on despite a depression after the loss of a loved one. Man could get surcease from his problems by going to sleep, provided he could fall asleep. There are built-in mechanisms for falling and staying asleep. Even the dream process, however disturbing at times, does work for man. Sleep since earliest times has been a wonderful state into which to escape, a remarkable repair station which enables an individual who is out of breath emotionally, so to speak, to catch it again. If I may quote Shakespeare briefly, "Sleep that knits up the ravell'd sleave of care." But this remarkable mechanism can be decompensated, even as Macbeth learned when he added, "Macbeth shall sleep no more."

Very early man learned that the fermented grape or starchy substance could produce a chemical which gave relief from anxious feelings. In larger doses it even produced sleep. Far back in the history of man, therefore, alcohol became available. The alchemist was present early on the scene to provide drugs from various botanical substances—deadly nightshade, the poppy, the hemp plant and others. In more recent times (1826) came the discovery of bromides by Ballard, of barbiturates by Baeyer (1863), and,

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most recently, that group of drugs which I have mentioned above, the tranquilizers. It was Bein who first described the peculiar property of reserpine as a sedative and hypnotic. He pointed out that animals would become tranquil and assume a resting position. They were never anesthetized, and could be aroused by acoustic or tactile stimuli. This observation has been confirmed subsequently in the laboratory, and the electroencephalographic differences between barbiturates and reserpine action in monkeys have been noted. The tracings of the animal under reserpine lacked the spindle and delta wave activity typical of barbiturate action, but the frequency of the reserpine rhythm suggested a stimulating effect on the reticular formation. In 1952–1953 Jean Delay and Peter Deniker in France noted that the drug, chlorpromazine, had a remarkable action in patients in agitated states as well as in those presenting symptoms of confusion. They utilized this substance to manage patients with schizophrenia, but usefulness was soon found for other conditions. More recently a third substance, meprobamate, with a myanesin-like action, was described as having a taming effect on monkeys and a quiescent effect on human beings. Although entirely different in its mode of action, it was said to have a certain component which resembled the quieting or "tranquilizing" effect of the other two drugs. Tranquilization thus became a nonspecific term describing the three substances, and later included groups of chemicals characterized by entirely different pharmacodynamic effects. Finally, all became known as the so-called "tranquilizing" or ataractic drugs, called by some "phrenotropic" or "psychotrophic." Chlorpromazine belongs to the phenothiazine group, and was the first of a number of derivatives from this basic structure.

The remarkable feature of the tranquilizing drugs is their complete dissimilarity in terms of chemical structure, yet their striking similarity in many aspects in action. Thus both reserpine and chlorpromazine reduce motor activity in experimental animals without inducing anesthesia. Hostility, if present, appears to be reduced by all three drugs, but in different degrees. Monkeys under reserpine and chlorpromazine can be handled without great difficulty, but under meprobamate will resist being manipulated. The catatonic-like picture following a high dose of reserpine or chlorpromazine is not seen after meprobamate, but the last in large doses will make the patient ataxic. Parkinsonian-like syndromes have occurred in certain patients after a course of reserpine or chlorpromazine, but are not seen with meprobamate. Reserpine is typically parasympathicomimetic, while chlorpromazine shows no particular shift in autonomic balance, although it has significant autonomic effects which are rather diversified. Both drugs (in large doses) will produce hypothermia. Meprobamate has no striking effect on autonomic function. Of the physiologic effects of the drug, the threshold to electroshock is lowered by reserpine, but meprobamate has a blocking action on electroshock. Chlorpromazine has a depressant effect on the diencephalic blood pressure regulation. We may also mention

that serotonin, an amine which allegedly plays a neurohumoral transmitter role in mental disease, is liberated from the central nervous system and intestinal tract by reserpine, but it is not affected by chlorpromazine or meprobamates. Many investigators have pointed out that, while it is impossible to find a basis in experimental pharmacologic evidence, the similarity of the tranquilizing action is such that both reserpine and chlorpromazine may be used interchangeably in many conditions. Meprobamate, on the other hand, is useful chiefly in the states of anxiety and tension associated with muscle spasm.

The difficulty is augmented when one moves from the laboratory of the experimental animal to the area of man. Thus one may set up a simple experiment in which five men are lined up at a bar. They are of equal weight and height—160 pounds each, measuring 5′ 10″ in height, and of comparatively similar body build. A bottle of bourbon whiskey is set in front of them. They all have jigger glasses of the same size and each man takes five drinks. What are the effects?

Man No. 1 becomes increasingly aggressive and finally offers to fight anyone in the room.

Man No. 2 becomes increasingly friendly and wants to talk with the other four, if they will only listen.

Man No. 3 becomes ardent and begins making passes at the waitress.

Man No. 4 becomes depressed and sits with his chin in his hands, staring straight ahead.

Man No. 5 gets sleepy and passes out.

Why the difference? They all took exactly the same substance. Why the five dissimilar responses? As is well known, alcohol, like any other drug of its kind, can only depress; it cannot stimulate. What do we mean by depression? We may use an analogy in a simple mechanism we all know, an automobile. If we were to exert a depressive action—that is, a retarding action—on the governor which prevents acceleration of a car, the car would actually go faster. In other words we would be retarding the retarder and therefore permitting speed-up.

The brain is made up of circuits or loops which are very elaborate. They feed backward or forward, reverberate, and send or receive from other circuits. Thus the brain is a system of balances and counterbalances which make possible the smoothing of motion, transmission of sensation and formulation of judgments. A movement like the flexing of a forefinger is not "simple." If we were to stimulate the hand or finger area of the motor cortex with an electric current, the forefinger would move, but not smoothly. There would be a quick jerk. Actually, we could not move the forefinger unless we were aware of it, and the motor cortex must receive signals from some part of the sensory cortex, particularly the parietal lobe, in order to initiate the movement. The motor cortex is nothing but a way station, an internuncial, so to speak. It feeds down through the pyramidal tracts and

finally reaches the region of the anterior horn cell. But again, an impulse in this pathway will induce only a jerk of the finger, not a smooth movement. Many tracts feed into the spinal cord—the tectospinal, the rubrospinal, the reticulospinal, the vestibulospinal and so on. They do not end directly on the anterior horn cell. They, with their fellow, the corticospinal tract, end along interneurones in the so-called internuncial pool, where they are met by certain synaptic resistances. As a result, there is a smoothing of the neural impulse, with, finally, a gradual feeding out to the anterior horn cell. Even the last is not a simple system. The anterior horn cells are made up of large fibers and a small one, the so-called gamma loop, all of which contribute to smooth motion and muscle tone.

This comparatively uncomplicated description pertains only to the wiggling of one finger. Think of how elaborate the brain mechanisms must be in what we subsume under the general term "behavior." Think of all the activity that goes on in our brain, asleep or awake. The number of circuits is infinite: the cortical and cortical-associational group; the diffuse thalamic projection system, with its feeding out of all of the somatic sensory and viscerosensory impulses; the reticular arousing system, which enables us to stay in the state of wakefulness or consciousness; the limbic system, with its role in the handling of feeling experiences, emotions—actually, a storehouse of previous experiences and "what to do about them." Add to these the autonomic nervous system and the neural humoral system, the brain in relationship to glands like the hypophysis, thyroid, adrenal and the like. All combine into a very complex, dynamic network, with feeds into and feeds back; there is an intake and an output. These internal communication circuits are loaded with engrams, neural pictures of life's experiences, all functioning at different levels of awareness, and each pattern is highly individual.

I think that the concept of level of awareness needs a bit of elaboration. For example, all of you are watching me and listening. Now that I call it to your attention, you become aware that your lumbosacral region is pressing into the back of the seat. Certainly this part of you, with a pressure of 100-plus pounds, was feeding signals into your nervous system, but they were coming in at a certain level. The signals were being filtered by the reticular formation of the brainstem, if you will. This magnificent system sorts information exactly as a digital computer combs data, but it is much more complex than our most elaborate electronic analyzers. Were we not to have this sorting system we would be overwhelmed by stimuli coming from without. We simply would not handle the flood of impulses pouring into us through every sensory modality. Suppose there were a splinter in your seat and it was digging into your skin. Certainly this new signal, which is coming in at a different intensity, would reach consciousness, whereas sitting in a smooth, comfortable chair does not reach awareness until I call it to your attention. This gives you an idea of the differential

filtration which can occur in one system alone, the reticular formation of the brainstem.

I review this, not to throw out large doses of neuroanatomy and neurophysiology, but to give you an idea of the complexity involved in the evaluation of a drug, if we are to have a true understanding of it. Into this elaborate mechanism of wires, relays and subcenters we throw a chemical substance—alcohol, barbiturates, bromides, tranquilizers—and we say, "The drug acts on the brain." Where on the brain? Are all brains the same? I have already mentioned that the engrams are as different as are people. Therefore, five men at the bar, with five brains similar anatomically, but with five dissimilar sets of life experiences, have five different reactions to the same drug. The fundamental action of any of these drugs, be they alcohol or reserpine, is the depression of part of the circuitry of the brain. The result is release, and what is released is that which is available. In short, the drug pulls the lid off of the Pandora's box of the nervous system, and whatever is contained in that box proceeds to tumble out. All lids do not come off the same way. The one that is drawn back by barbiturates, which depresses high cortical activity and produces sleep, is quite different from that removed by the tranquilizers, which work through the reticular formation and which, in ordinary doses, do not affect high cortical activity.

Dosage is another factor. A small dose of alcohol, by depressing cortical-associational circuits that participate in the process of anxiety, tension and the like, releases the person, so to speak, so that functionally he is better. In our laboratory, one of our investigators, Dr. Harvey Nash, has been able to show that small dosages of alcohol produce more rapid, more accurate mathematical calculations, faster and better judgments. However, larger doses slow down reflex activity, interfere with motoric execution, impair judgment and, finally, scramble the entire cerebral response.

One cannot evaluate drugs in human beings without taking into consideration the so-called placebo effect. In late 1955 an interdisciplinary team, composed of a psychiatrist, an internist and an anesthesiologist at Northwestern University Medical School, performed a carefully designed experiment on "The Effect of Rauwiloid on Preoperative Anxiety." Thirty patients on the surgical service were selected at random. Operative procedures to which they were to be subjected varied from varicose vein ligation to abdominal-perineal resection. Most of the patients required general or spinal anesthetic, although five were operated upon under local. Rauwiloid was given six days prior to surgery in a concentration of 6 mg. per day. Half of the patients received the active drug; half were given an identical but bland pill prepared by the same pharmaceutical house. Neither the doctor, the nurse nor the patient had any idea of exactly what was being administered, a true double-blind experiment. The code was broken at completion of the study. The patient's self-assessment was evaluated. He was interviewed by the psychiatrist at six days and one day before and one

day after operation. He was also interviewed regularly by the nurse and anesthesiologist. The observations of the last two were either anecdotal or so deviant that they could not be utilized for integration into final results. Data on 29 patients of the 30 could be quantified at the end. One patient had to be dropped from the experiment because of marked blood pressure fall. There was absolutely no difference between the two groups, those receiving the active drug and those the inert substance. The patient whose blood pressure fell precipitously was taken off of the medication at the insistence of the Chief of Surgery. When the study was ended it was discovered that this particular patient had been on the placebo. It was interesting that, in the placebo group, two patients had a significant drop of blood pressure, 10 remained unchanged, and two had an increased blood pressure.

A striking aspect of the outcome is that 28 out of 30 patients, by their own rating, considered themselves to have been improved by the medication. This was in comparison with patients who were not in the experiment. Since the sole difference between this group of patients and any other 30 patients in surgery was the fact that there was a high level of communication between patient and doctor, the only conclusion that could be reached was that the subjective improvements in the patients resulted from patient-doctor relationship. The placebo was merely part of the language of communication. Although the doctor did not express it overtly, it would seem that all patients got an idea from general contact with him that they were being handled in a way to alleviate their preoperative anxiety. In this relationship they obtained information about the nature and timing of the surgery. This was very reassuring to all of them, and was apparently the most effective therapeutic agent in the test.

This experience is not new. Other studies would indicate that placebo effects are not imaginary, nor are they results of suggestion. The investigations of Stewart Wolf have been particularly revealing, and his conclusions would indicate that the mechanism responsible for placebo responses is connected with circuits in the cerebral cortex. All placebo experiments, to eliminate suggestion, must be blind, because the physician, too, must not know whether he is giving a strong drug or a control. One of Wolf's favorite examples is that of a patient who had suffered from chronic asthma for 27 years, with almost continuous attacks for 17. He had been a useful subject on whom to test new drugs. Finally, a product of a pharmaceutical house seemed to be effective. When he was given the agent he was free of asthma; when it was stopped the asthma returned. When the doctor substituted a placebo without the patient's knowledge, the asthma was not relieved. Shifts from agent to placebo, and from placebo to agent, were carried out several times with consistent results, always in favor of the agent. When the company was approached for an additional supply of medication, their representative acknowledged that they had had so much trouble with positive enthusiastic reports that in this instance they, too, had sent a placebo.

The doctor knew nothing of it, nor did the patient, who was doing beautifully on a bland substance even though he had failed on the doctor's own placebo, which apparently had been presented in a way that left the message that it was an inert substance.

One very striking experience of my own has given rise to the use of a group of drugs in our psychiatric unit which we call plá-cebos. This is spelled exactly like the word "placebo" but is pronounced "plá-cebo." They are in a completely different category for us. We make them up in specially colored capsules and use them only in the most refractory situations. Plácebos at our hospital came about thus: A schizophrenic girl of 17 had been admitted in an acutely disturbed state. On admission she was continuously noisy, destructive and violent. In the previous 24 hours she had received over 40 gr. of sodium amytal, which had served only to excite her. She had been started with 3 gr. When this failed the family doctor had added six more. When this did not quiet her he injected the drug intravenously until she quieted down, but this had required almost 15 gr. The effect wore off in an hour or less, and she became wild again. He gave her more by mouth, but this did not help, and this went on until he had reached 40 gr. He was fearful of going any further, and finally advised the family that she had better be hospitalized. We spent four difficult days with this girl as we permitted the excitement to wear off without benefit of sedation while preventing her from thrashing herself to exhaustion. Drug withdrawal was finally achieved and she quieted down. However, she was a behavior problem about the ward and continuously in trouble. Her intelligence was unusually high, and she was very "crafty" in her actions. For example, she surreptitiously obtained parts of a nursing uniform from the room where the girls changed, one garment at a time, usually uniforms of the women who were off duty. One day, dressed in a nursing uniform, during a period of excitement with another disturbed patient she helped in the care of the patient and left with the rolling cart, helping to transport the patient to the x-ray department. While everyone was involved in searching for her, this girl, unobtrusive in a proper uniform, made her way into the nursing station, obtained her chart and read her history. Here she apparently learned that she had been on various medications previous to entry, and that the excitement had subsided under "placebo" therapy. She discovered that she was sleeping well on these "placebos," whatever they contained. That night she appeared at the nursing station and demanded her sleeping medicine with the words, "I don't want Seconal; I don't want Nembutal; I don't want sodium amytal; I don't want Thorazine; I don't want Serpasil; I don't want chloral; I don't want any tranquilizers. I want my own medication, my plácebo. I want the same stuff I've had the last two nights, 'Plácebo.'" When this was given her, she slept soundly. We tried her subsequently on sodium amytal, 6 gr., Nembutal, 3 gr., and Seconal, 3 gr., but she could not fall asleep. She had become obedient, and would take whatever medication

was offered, but she slept only on her pink plácebo. Therefore, when we have a patient now who is particularly sleepless, we simply give him the pink capsule and, in most instances, the patient sleeps. I must admit that there is a strong element of suggestion here, because on our service the patients learn from each other about the power of the pink medication. They do not know the word placebo; they simply refer to it as "the capsule that passes you out."

This was not my first experience with this type of medication, or with the fact that some of the so-called powerful drugs, hypnotics like the barbiturates, actually may excite more than they depress, particularly after they have been given in repeated small dosages. In the early days of the North African campaign, when our armies were green, we had great difficulty with battle reactions. Our boys were not combat-wise. They were not accustomed to shell fire. They certainly were not prepared for the high velocity German 88, where the shell reached them and exploded long before the noise of the shot or the whistle. These shells left the muzzle at a speed three times that of sound, and the byword in the theatre was, "If you hear the whistle, you're safe." Too many men had seen the flash of the explosion long before they heard the whistle, and they were quite unnerved by the experience. In addition, the Stuka dive bombers were terrorizing. The death of companions, the demoralization of forces, as in the debacle of Kasserine Pass, were events for which the young American soldiers had never been prepared. It never occurred to them that an American Army unit could be defeated in combat. Therefore, these men arriving at the first evacuation level were tense and shaky, and showed various types of neurotic and pseudopsychotic behavior. They were given a sedative and evacuated. At the next level they were given another sedative and evacuated further to the rear, step by step, until they reached us at the general hospital level. By this time the pattern of the emotional reaction was established. They were at a base sector that was comparatively quiet, except for an occasional bombing, or gunfire as our troops practiced for the next invasion or our planes and submarines practiced detection tactics. The days were comparatively safe, but the men feared the night. They were afraid to sleep because this meant battle dreams. Their requests at bedtime were most revealing. Early in the war, our nurses walked around the ward with a bottle of sodium amytal. The continual plea from the soldiers was, "Please, don't give me blue heavens. Don't make me take blue heavens. They give me battle dreams." At first our nurses insisted, and the men obediently took the drug. Every night we had trouble. The dropping of a chart, a loud footstep or a flashlight beam would cause the soldier to drive out of bed onto the terrazzo floor and rip at the stone with his bare fingernails, which bled as he tried to dig a foxhole in the tile. When we gave him no medication he gradually settled down after several days, except for a few who had had what was essentially a psychotic reaction and required special treatment.

In late 1942 and early 1943 I met the best "tranquilizer" I have ever encountered, a young nurse who had a remarkable ability to put a ward of anxious soldiers to sleep. This young woman, whom we may call Miss R., never used drugs. She became the toast of the Fifth Army; her reputation spread rapidly, and at night in our ward I would always hear the call, "Miss R., come tuck me in," "Miss R., come straighten my pillow," and this she would do. She would tighten a blanket, she would fluff up a pillow, she would tuck a soldier in here and there, she would pat one man on his seat; she might lean over and give another man a light kiss on his cheek, at his request, and in a short time 30 or 40 men would be sound asleep, I am sure dreaming not of battle but of Miss R.

This tranquilizing of people by a loved one or by some symbol is as old as man. Who among you has not heard the call, "Mommy or Daddy, come tuck me in," and when that act is completed, little Bobby, who has been bouncing all over the bed, goes to sleep. How many times have you seen an older child, even late adolescents, call down as you open your house door at midnight, "That you, Daddy? Goodnight." He will admit to you the next morning that he could not sleep until you got home, but the moment you opened the door he became drowsy and was able to fall asleep. How many devices are used for tranquilization—hot milk, Ovaltine, a bunch of grapes, even crackers.

The question then arises, "Shall we use drugs?" and the answer is, "Of course, where the situation demands it." Certain general rules must be kept in mind. Aging brains, for example, do not tolerate powerful sedatives well. This produces confusion. Clow has shown that if 100 confused, psychotic old people are placed in a good hospital setting, one which is friendly, and considerate of all their physical and emotional needs, and if they are given reassurance repeatedly and taken off of all drugs, I repeat, *all* drugs, at least 60% will clear. An old person who becomes confused at night is much better off with a 15-watt baseboard light which enables him to orient himself if he awakens at 2 a.m. to go to the toilet than he is with a drug that knocks him out so that he sleeps all night. A drug only adds a daytime confusional state to the nighttime sensory deprivation bewilderment. Certain drugs, like Seconal and Nembutal, when taken in large doses over a long period of time, may have a dangerous sequel. If the individual is suddenly taken off of medication he may develop a withdrawal syndrome, with convulsions and psychosis. I have seen this many times, and the condition was recently described in the *Journal of the American Medical Association* by D. Harris Isbell, of the U. S. Public Health Service at Lexington Hospital for the Narcotically Addicted. One has only to see the effect of large doses of barbiturates on the electrocorticogram to realize that a disturbance in brain rhythm may ensue when, after prolonged intake, a drug is suddenly discontinued. If a patient has a convulsive diathesis and is on large doses of phenobarbital, the sudden removal of the drug may cause

him to go into status epilepticus. In short, the barbiturates, while commonly used, are not entirely benign. Bromides in large doses may produce intoxication, and descriptions of this state go back to the middle of the 19th Century, when the drug-induced confusional state simulated the then common general paresis. Many a diagnostic error was made by the unwary. We still see bromide psychosis, and not infrequently, because substances containing bromides may be sold over the druggist's counter.

The effect of the drug depends upon the level of the symptom to be relieved. If a patient starts with intense pain, morphine is about 75% effective. A placebo given to that patient is about 35% effective. In other words, the placebo equals 50% of our most powerful drug, morphine. If he has only moderate pain, morphine is about 52% and a placebo only about 40% effective. As the pain becomes less severe, the placebo benefit drops to 29%. If a patient is very anxious, any drug is about 60 to 70% effective, and the placebo is close to this figure. A large wound in a soldier, his safe ticket home, is often a powerful tranquilizer. He complains of no pain; he does not ask for drugs. Weeks later, with the wound almost healed, and the prospect of return to duty looming, anxiety and sleeplessness set in. He begs for sedatives for the day, sleeping medication for the night.

Therefore, where do we stand with these so-called tranquilizing drugs, the reserpine group, the phenothiazine derivatives, the meprobamates? I shall not even begin to attempt to review the literature on these. Two years ago almost 6,700 articles had been written on chlorpromazine alone. There have been many symposia on these drugs—those of the New York Academy of Science, the American Association for the Advancement of Science, the Association for Research in Nervous and Mental Diseases, and the International Conference in Psychiatry, in Zurich, Switzerland, 1957. Their mode of action has been described in these publications, and I believe that it is worth while to own these books, so that references on the important experimental work going on in this field are at hand. It is essential to keep in mind that these drugs may exert their clinical effects of quieting or tranquilizing without the severe depression or the heavy sedation characteristic of other drugs, like the barbiturates or opiates. Some of the hyperreactivity of the tense or anxious patient may be due to excessive transmission of sensory information along neural pathways without effective selection or control. Drugs like chlorpromazine, by increasing reticular input and conduction, and thus enhancing this remarkable filtering mechanism that I have described, may act to reduce the inflow of information which is of no importance to the organism and which serves only to disturb.

On the other hand, such drugs should not be used arbitrarily only to control a symptom. A patient who is vomiting should not be given chlorpromazine to control it before the physician has learned why he is vomiting. I have seen several instances of brain tumor where the vomiting caused by the neoplasm was treated with this drug and no systematic attempt

made to learn the cause for the symptom. On the other hand, the post-occipital muscular pain called "headache," in a person under tension, yields much more effectively to meprobamate than to codeine. A hypotensive patient who is tense and anxious is much safer with reserpine than with chlorpromazine, which may augment the blood pressure drop, but the patient with an agitated depression may do better on chlorpromazine than on reserpine, because the latter has been known to precipitate or aggravate latent depressions. Chlorpromazine in large doses may produce a parkinsonian-like state, but this is easily reversed by stopping the drug, and one should always keep in mind that among the phenothiazines, chlorpromazine is the most likely to produce liver damage and jaundice.

One cannot pick up an article on the tranquilizing drugs without reading their effect on psychotic patients, that tremendous group of neglected people who fill more hospital beds than all other patients combined. Many of you have read reports like the following: "In this study of the effects of the drug, 85 patients were treated; 50% showed a decided improvement and 75% benefited to some extent. Patients showing soiling, wetting and destructiveness became more cleanly, less destructive and better able to care for themselves, and patients given to outbreaks of violence became better adjusted with their environment, and their activities are more easily directed into useful channels following treatment. Patients requiring tube feeding take food voluntarily after two to three days. The most lasting improvements are found in those cases previously regarded as having a favorable prognosis. When one considers the change in the environment of the patients not treated, shown by lessened disorder, confusion and untidiness together with a conservation of energy to the nurses and other employees, the results are still of greater value. There is marked reduction in the waste of clothing and bedding from soiling and tearing and fewer articles have to be repaired and laundered; fewer nurses are required to care for the disturbed patients. One nurse said, 'Before these patients were treated, we had to struggle with them every morning to get them bathed and dressed. Fights were frequent occurrences. By the time the patients were bathed and dressed, we were all tired out struggling with them before the real day's work had begun. Before the treatment was begun it took four and five of us to bathe and dress these patients. Now I can supervise the bathing and dressing of these patients alone.' "

This report is not describing chlorpromazine or any of the other phenothiazines; it is not describing the results of reserpine or any of the Rauwiloid products; it is not describing meprobamate. This is a 1926 report in the *American Journal of Psychiatry* on the use of bromides in psychoses in a State hospital. I have seen similar reports in mid-19th Century French and German literature on bromides and opium.

We may properly ask, then, Has anything new been added? and the answer a categoric Yes. In the last 10 years we have become familiar with

a large group of drugs which enable us to handle many conditions which heretofore we had had to treat with more sedative, more depressing, more hypnotic and more confusing drugs. Our patients are clearer now, and are able to go about their business more effectively. Yet the very volume of the drugs that are sold frightens one. Too many patients start with a doctor and then continue treatment on their own. They obtain the drug over the counter or by prescription, and take more and more until they reach tremendous doses. I have seen dosages up to 4,000 mg. of chlorpromazine daily. I learned that some patients admitted to the psychiatric unit at Bellevue Hospital in New York have gone up to 11,000 to 12,000 mg. I heard of one instance in Texas, which is never to be outdone, where a patient was taking almost 15,000 mg. daily!! Too many patients are prescribing these drugs on their own. There are dangers, there are limitations—and proper precautions should be established. Similarly, there are many instances where a doctor dealing with a functional problem handles the symptoms by prescribing a tranquilizing drug, rather than sit down with the patient to learn what is causing the anxiety. This sets up the vicious cycle of making the patient dependent upon a drug, and never comes to grips with the basic emotional difficulty underlying the symptom.

Therefore, to summarize, the tranquilizing drugs are very useful and, comparatively speaking, are safe. They are not miracle drugs, our newspapers and lay magazines notwithstanding. They are therapeutic substances, and thus are welcome in our medical armamentarium. They are to be employed in symptomatic treatment; they are not curative of specific conditions in the sense that quinine can be used for the cure of malaria, or penicillin for pneumonia. They merely handle the disturbance in the neural communication system. They are useful in that they render the patient more available for approach by the physician, who may then be able to communicate with the patient and get to the underlying cause. In short, these drugs are tranquilizers, or facilitators, but they are never a substitute for a full doctor-patient relationship.

SUMMARIO IN INTERLINGUA

Drogas destinate a impartir al individuo un senso de pace es in uso depost tempores immemorial. Tales es alcohol, opiatos, e le gruppo solanacee, sed etiam cannabe, bromuros, e barbituratos, e plus recentemente un nove gruppo de drogas designate como "tranquillisatores".

Differente drogas ha differente sitos de action in le systema nervose central. Durante que substantias como le bromuros e barbituratos impinge principalmente super le cortice, le plus recente compositos affice plus basse structuras, como le formation reticular. Etiam ab le puncto de vista clinic, le effectos notate differe ab un droga al altere. Le si-appellate sedativos produce un obtusification general e mesmo somnolentia. Le plus recente compositos, in dosage ordinari, es libere de tal effectos. Isto vale specialmente con respecto al drogas del familias rauwaloide e phenothoazinic. Le meprobamatos produce lor effecto tranquillisatori per afficer le musculo. Illos effecta un stato de relaxation comparative.

Tamen, le homine non es un simple subjecto pro le evalutation del effectos de

drogas, proque un substantia particular—per exemplo le alcohol—evoca varie reactiones in varie individuos, mesmo quando illo es prendite in comparativemente equal doses. Isto se explica per le facto que tal drogas—in nostre exemplo le alcohol—exerce lor effectos per deprimer le neuro-activitate superior, con le resultato que le cosas que se trova infra, sia que sia, es liberate. Viste que il non pote occurrer que duo personas ha habite exactemente le mesme typos de experientia e que, per consequente, il non pote occurrer que duo personas ha exactemente le mesme circuitos intracerebral, le resultante comportamento va differer ab un individuo al altere. Le dosage es un altere factor. Micre quantitates de un substantia como alcohol deprime le circuitos cortical que participa in le manifestationes de anxietate e imparti al individuo un senso de exhilaration. Plus grande doses induce un stato de depression; ancora plus grande, mesmo somnio.

In evalutar le effecto de un sedativo o de un agente tranquillisatori, on debe poter evalutar le individuo super le qual le droga exerce su effecto, le importantia—in su caso—del factores active in suggestion, le efficacia de placebos, etc. Mesmo le plus caute experimento cec o duple-cec debe esser controlate pro assecurar que le examinator non produce un effecto, sin voler lo, in consequentia de su proprie attitude verso le substantia investigate. In un situation in que omne le variabiles es stabilisate, un placebo es frequentemente tanto efficace como un potente sedativo o tranquillisator. Isto esseva le experientia del autor durante le secunde guerra mundial. Le sedativo le plus universalmente efficace es le presentia de un persona amate o un acto executate per un tal. Per exemplo, arrangiar le lecto pro un infante, sequite per un basio o un caressa, o render possibile le association de un action con un expression de amor e establir assi un ambiente de securitate—un vitro de lacte, un portion de ovomaltina, o un racemo de uvas presentate per un persona amate—suffice frequentemente pro producer somnio.

Le impacto confusional de drogas super le cerebro de personas plus tosto vetule es etiam discutite, e le importantia de usar sedativos in quantitates minimal es sublineate. Le effecto de un droga depende etiam del nivello del symptomas que debe esser alleviate. Quando un patiente suffre intense grados de dolor, un placebo ha circa un medietate le potentia de morphina. Quando le dolor es leve, un placebo ha solmente un quarto le efficacie de morphina.

Tamen, le drogas tranquillisatori representa un importante addition al armamentario therapeutic, e le melior es considerar los como substantias que promove le action del formation reticular del trunco cerebral. Iste systema reduce le influxo de signales ab le exterior. Illo interrumpe le stimulation del systema nervose e resulta assi in un effecto de tranquillisation. Tamen, tal drogas non deberea esser usate como sol medio in le suppression de un symptoma particular—per exemplo vomito—sin primo essayar un clarification del etiologia del symptoma. Il occurre frequentemente que le plus importante base pro le establimento de un diagnose de serie conditiones, per exemplo le imminentia de apoplexia cerebral o le presentia de un precoce tumor cerebral, es perdite proque un droga como chlorpromazina ha supprimite lo.

Le drogas tranquillisatori per se non es narcomanificante, sed il semper existe subjectos qui es preste a formar un habitude. Post que illes ha recipite un certe substantia un sol vice e post que illes lo ha trovate salve, illes comencia—sin guidantia o autorisation—usar lo in crescente doses usque lor consumption attinge nivellos massive. Un tal disveloppamento debe esser discoragiate.

In summa, le drogas tranquillisatori que esseva disveloppate in le curso del passate decennio es substantias de grande valor, specialmente pro le tense patiente in stato de anxietate. Illos es utile in le tractamento symptomatic de certe disordines associate con disturbationes neural. Illos exerce pauc effecto super le cortice sed produce lor action tranquillisatori per afficer le centros inferior del trunco cerebral. Illos es, per consequente, substantias de valor indubitose que debe esser administrate per un experte practicante de medicina.

ANALGESIC EFFECT OF DEXTROPROPOXYPHENE HYDROCHLORIDE IN ELDERLY PATIENTS WITH CHRONIC PAIN SYNDROMES * †

By R. W. Boyle, M.D., F.A.C.P., C. E. Solomonson, M.D., and J. R. Petersen, M.D., *Milwaukee, Wisconsin*

Pain is the symptom for which people most often seek medical attention. The relief of pain resulting from nonprogressive chronic illness has been difficult, since the agents most effective in the relief of such pain have in common the most undesirable side-effect, that of addiction. The search for an effective, non-narcotic analgesic has been stimulated by a need for an agent efficacious in the relief of chronic pain, yet free from the disadvantages of the opiates and their derivatives.

Recently a new analgesic agent, dextropropoxyphene hydrochloride (Darvon),‡ has been introduced for use by the medical profession. Clinical trials have indicated that dextropropoxyphene hydrochloride is effective and not habit-forming in long-term usage and has only minor gastrointestinal reactions as undesirable side-effects. It is the purpose of this study to compare the effectiveness of dextropropoxyphene hydrochloride with analgesic agents of established potency in a group of geriatric patients who have medical conditions giving rise to pain of a chronic nature.

Methods

This study was carried out with a group of patients hospitalized at the geriatric and chronic disease division of Milwaukee County Hospital during the period February 1, 1958, to January 31, 1959. These patients required long-term hospital care but did not need the close medical supervision of a general hospital or frequent alteration of their therapeutic program. They had medical problems in the following general categories: fractures, rheumatoid arthritis, osteoarthritis, cerebral vascular disease with hemiplegia, previous amputation for complications secondary to peripheral vascular disease, and miscellaneous conditions. The patients selected had illnesses, as noted, which were of a chronic, relatively stable nature and commonly produce chronic pain. This was established by interviewing the patients carefully, prior to selection. In some instances, several interviews were necessary to establish clearly the presence and the severity of the pa-

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‡ Supplied as Darvon by J. M. Maas, M.D., Lilly Research Laboratories.

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tient's pain. Patients who required morphine, meperidine or drugs of similar potency, and psychophysiologically disturbed patients were not included in the study. If, after he had been in the group being studied for a short while a patient was felt to have few symptoms warranting analgesics, his medications were steadily decreased and he was removed from the group. This was also true for patients whose physical status was improving with therapy.

Procedure

The analgesic effectiveness of six pairs of agents was studied:

Codeine, 65 mg., and placebo, 325 mg.
Codeine, 32 mg., and aspirin, 325 mg.
Dextropropoxyphene hydrochloride, 65 mg., and placebo, 325 mg.
Dextropropoxyphene hydrochloride, 32 mg., and aspirin, 325 mg.
Aspirin, 650 mg.
Placebo, 650 mg.

Each pair of drugs was prepared in capsules of identical size and external markings. The paired medications were given as two capsules, because the total quantity of the dose was too great for a single capsule. The hospital pharmacist gave each pair of analgesics a code number, and each individual member of the pair had either an R or an L designation. The final contents of each of the six pairs of agents tested were known to the pharmacist alone, who disclosed the code used only after the results of the study had been analyzed. When an analgesic dose was ordered, the patient received two capsules, one with the R designation, the other with the L designation. The authors selected the patients, ordered their analgesics while the patients were being studied, and followed the patients, observing and recording their subjective reactions daily. The men were selected and followed by one observer, the women by another.

Any analgesic which the patient had been receiving prior to the study was discontinued and replaced by the analgesic pair. Many of the patients had been on no consistent analgesia prior to entering the study, but were symptomatic. Some were receiving tranquilizing agents, and these were not discontinued during the time the patient was on the study. The pair of analgesics was ordered for the patient as frequently as his symptoms seemed to warrant. The usual frequency of dosage was from two to four times daily. One pair of analgesics was studied for from five to seven days and then, unknown to the patient, another pair was substituted. The sequence of pairs studied varied with the two groups, males and females, but each observer maintained the sequence of the pairs of drugs he was using once it was established. Each patient in a group was seen once daily by the observer, and his reactions and symptoms for the preceding 24 hours were discussed with him, along with his progress.

The patient's symptomatic response to the pair of analgesics which he was receiving was graded as "worse," "no appreciable effect" or "good."

It was felt that no further delineation in grading the subjective responses in this group of patients was possible. Ancillary changes in the patient's condition and symptoms other than analgesic effectiveness were recorded on the data sheet.

Each patient remained in the study group until he (1) had minimal symptoms requiring no consistent analgesia; (2) had progressive symptoms not relieved by the full doses of the drugs studied; (3) wanted to discontinue the medications; (4) became erratic in taking medicines, or (5) had undesirable side reactions. After a patient had received each of the six pairs of agents being studied, for three test periods, he was removed from the group and, if necessary, returned to his previous medications. The reactions of patients who had successfully taken three or more pairs of the agents studied were considered to be suitable for statistical analysis.

Results

One hundred twenty-one patients who had chronic pain were studied. The responses of the patients who received three or more pairs of the analgesics form the basis of this report. Eighty patients received three or more pairs of the analgesics. There were 29 males and 51 females in this group. The average age of the men was 65 years, with a range of 44 to 87 years, and the average age of the women was 71 years, with a range of 45 to 88 years.

These patients had the following major diagnoses:

Fractures (arm, leg)		*Amputations*	
Male	3	Male	11
Female	2	Female	2
Total	5	Total	13
Fractures (hip)		*Rheumatoid Arthritis*	
Male	5	Male	0
Female	11	Female	7
Total	16	Total	7
Cerebral Vascular Accident		*Osteoarthritis*	
Male	3	Male	3
Female	8	Female	11
Total	11	Total	14

Miscellaneous	
Male	4
Female	10
Total	14

The number of patients falling under each diagnostic category is too small to subject to statistical analysis.

The following data express the daily response of the patients in total patient days as to medications, given as "worse," "no effect" or "better":

Medication Pair		Worse	No Effect	Better
1. Codeine, 65 mg.	Male	43	106	157
	Female	50	223	214
2. Dextropropoxyphene hydrochloride, 65 mg.	Male	35	112	107
	Female	59	268	190
3. Codeine, 32 mg., and aspirin, 325 mg.	Male	39	96	144
	Female	23	202	222
4. Dextropropoxyphene hydrochloride, 32 mg., and aspirin, 325 mg.	Male	47	82	110
	Female	18	209	159
5. Aspirin, 650 mg.	Male	37	119	124
	Female	49	217	197
6. Placebo	Male	77	153	77
	Female	68	200	163

These patient responses were then analyzed, using Ridit transformations:[1]

Medication Pair	Worse	No Effect	Better	Total	Mean Ridit
1. Codeine, 65 mg.	93	329	371	793	0.521
2. Dextropropoxyphene hydrochloride, 65 mg.	94	380	297	771	0.484
3. Codeine, 32 mg., and aspirin, 325 mg.	62	298	366	726	0.556
4. Dextropropoxyphene hydrochloride, 32 mg., and aspirin, 325 mg.	65	291	269	625	0.509
5. Aspirin, 650 mg.	86	336	321	743	0.506
6. Placebo	145	353	240	738	0.436
Total	545	1987	1864	4396	
Ridit	0.06199	0.34998	0.78799		

Variance Analysis

Source	Sum of Squares	*df*	Mean Square	*F*
Rx	5.220	5	1.044	15.35
Error	298.656	4390	0.068	
Total	303.876	4395		

Comparison of Treatments

Pair	Mean Square	*F*
6 vs. 2	0.867	12.75
3 vs. 1	0.468	6.88
2 vs. 4	0.212	3.11
2 vs. 1	0.552	8.12
5 vs. 1	0.145	2.13

Variance analysis indicates that significant (p less than 0.01) differences in response occurred among the medications.

When the effects of medication are paired and compared, one finds that codeine, 32 mg., with aspirin, 325 mg., is reported to be significantly better and the placebo significantly poorer than any of the other agents studied. The other pairs of analgesics were also reported as different, i.e., codeine, 65 mg., was not different from dextropropoxyphene hydrochloride, 32 mg., with aspirin, 325 mg., or from aspirin, 650 mg., but was better than dextropropoxyphene hydrochloride, 65 mg. No significant changes were found between dextropropoxyphene hydrochloride, 65 mg., dextropropoxyphene hydrochloride, 32 mg., with aspirin, 325 mg., and aspirin 650 mg.

Discussion

It is well known that relief of pain, a subjective experience, is difficult to evaluate. In a study of this type the response—i.e., "worse," "better" or "no change"—is gauged by the observer's awareness of the patient as a total being. Thus, the observer must evaluate not only what the patient states but also how he describes his experience. Included would be other, rather intangible facets, such as expression and posture; however, these factors do not preclude a reasonably accurate appraisal of the patient, provided patients' responses are classified in broad categories. Despite these limitations, many investigators feel that analgesics are best evaluated under conditions similar to those in which they are going to be used clinically, and that data obtained from animal experiments, or when a measured stimulus is used, are not entirely valid.[2] This we have done in comparing dextropropoxyphene hydrochloride with analgesics which have been well studied. A "double-blind" technic of the usual design was employed in this study. The observer did not know the pair of analgesics the patient was receiving, but he did know when one pair was substituted for another. This admittedly is a potential source of error, but we do not believe it has greatly altered the results obtained.

We have demonstrated the efficacy of the combination of codeine, 32 mg., with aspirin, 325 mg., already well established. We have also demonstrated that aspirin, 650 mg., dextropropoxyphene hydrochloride, 32 mg., with aspirin, 325 mg., and codeine, 65 mg., are equivalent in analgesic potency. Codeine, 65 mg., was shown to be more effective than dextropropoxyphene hydrochloride, 65 mg.

Throughout the study there was a very low incidence of gastrointestinal side-effects. This is interesting, because it is known that codeine will frequently produce nausea and vomiting. Only four patients had to be removed from the study because of nausea and vomiting. It was found that three of these patients had been receiving dextropropoxyphene hydrochloride, 65 mg., three times daily for from three to four days. Two of the three patients had rheumatoid arthritis and poorly controlled diabetes mellitus.

It would be difficult to determine whether the gastrointestinal disturbance in these two patients was secondary to diabetic control or to the dextropropoxyphene hydrochloride. The fourth patient had nausea and vomiting after receiving 65 mg. of codeine three times daily for four days. No other side-effects were noted.

Summary

The analgesic effectiveness of dextropropoxyphene hydrochloride was studied in a group of patients in the geriatric age group who were experiencing chronic pain. Dextropropoxyphene hydrochloride was compared with other established analgesics—codeine and aspirin, and combinations thereof.

It appears that, among the agents studied, the analgesic potencies of dextropropoxyphene hydrochloride, 32 mg., with aspirin, 325 mg., and of codeine, 65 mg., and of aspirin, 650 mg., are equivalent. We also observed that the most effective analgesia obtained was with a combination of codeine, 32 mg., and aspirin, 325 mg.

Summario in Interlingua

Le efficacia analgesic de hydrochloruro de dextropropoxyphena (Darvon), acido acetylsalicylic, codeina, e placebo—sol e in varie combinationes—esseva studiate con le uso de un technica duple occulte. Cento vinti-un patientes, hospitalisate in un establimento geriatric, esseva evalutate. Illes habeva syndromes de dolor associate con chronic e relativemente stabile morbos medical. Le patientes esseva observate diurnemente e lor responsas esseva marcate como "pejor", "nulle alteration", e "melior". Le drogas e combinationes de drogas esseva administrate in capsulas de apparentia identic e esseva alternate—al inscientia del patientes—a intervallos de inter cinque e septe dies.

Octanta patientes—51 feminas e 29 homines—recipeva tres o plus del drogas studiate. Il es iste gruppo de patientes qui representa le base del presente reporto. Acido acetylsalicylic in un dosage de 325 mg con 32 mg de codeina esseva significativemente melior que le altere combinationes studiate. Placebo esseva significativemente pejor. Esseva notate pauc differentia in le efficacia de 65 mg de codeina, 32 mg de hydrochloruro de dextropropoxyphena con 325 mg de acido acetylsalicylic, e 650 mg de acido acetylsalicylic. Codeina in un dosage de 65 mg esseva plus efficace que 65 mg de hydrochloruro de dextropropoxyphena.

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COMBINED CLINIC

THE LYMPHOMAS: COMBINED CLINIC AT THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK, N. Y.*

Moderator: ALFRED GELLHORN, M.D.; *Discussants:* CHARLOTTE FRIEND, Ph.D.,† JOHN E. ULTMANN, M.D., and PHILIP FEIGELSON, Ph.D., *New York, N. Y.*

DR. ALFRED GELLHORN: Today we discuss a group of diseases, the lymphomas, various aspects of which are being productively investigated in many parts of the world. During our presentation we will introduce summaries of some phases of these investigations not only because they illuminate hitherto obscure facets of the lymphomas, but also because they have relevance to other malignant neoplastic diseases and increase our understanding of biologic phenomena in normal cells as well.

To set the stage for certain issues to be highlighted, I would like to offer a kaleidoscopic review of the natural history of the malignant lymphomas. Hodgkin's disease and lymphosarcoma are the tumors encompassed by this designation. The precise differentiation between these two major entities rests on histologic characterization, despite many differences in the clinical course. Both Hodgkin's disease and lymphosarcoma have been further fragmented morphologically, but in the case of the former, such additional classifications carry no implications regarding the course of the disease and are therefore of no real clinical value. The subdivision of lymphosarcoma according to histologic criteria does carry information about the course to be anticipated and problems peculiar to each type. A simple classification into three types consists of giant follicular, small cell or lymphocytic, and large cell, both lymphoblastic and reticulum cell.[1]

The lymphosarcomas can affect all age groups; however, the frequency distribution when plotted against age is skewed to the right, the peak frequency rising abruptly between the fourth and fifth decades, and declining more gradually to a low but appreciable incidence from the sixth decade on. The three histologic variants have a random distribution within this frequency curve.

In one-half of patients with lymphosarcoma, initial clinical recognition occurs with enlargement of one or more groups of subcutaneous lymph nodes. In

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the other half, there may be lymphadenopathy within the thoracic cavity or retroperitoneal space which makes itself known because of pressure on adjacent structures, or there may be infiltration of organs such as the spleen, liver and gastrointestinal tract which presents as palpable abdominal tumors or leads to functional disturbances. Once the lymphosarcomas have been recognized, the course is usually characterized by apparent waves of dissemination and intervals of relative quiescence. As more and more of the structures of the body become involved, anatomic and physiologic distortions occur and, as a late phase of the disease, the frequency and severity of constitutional manifestations grow, until ultimately the host is overwhelmed.

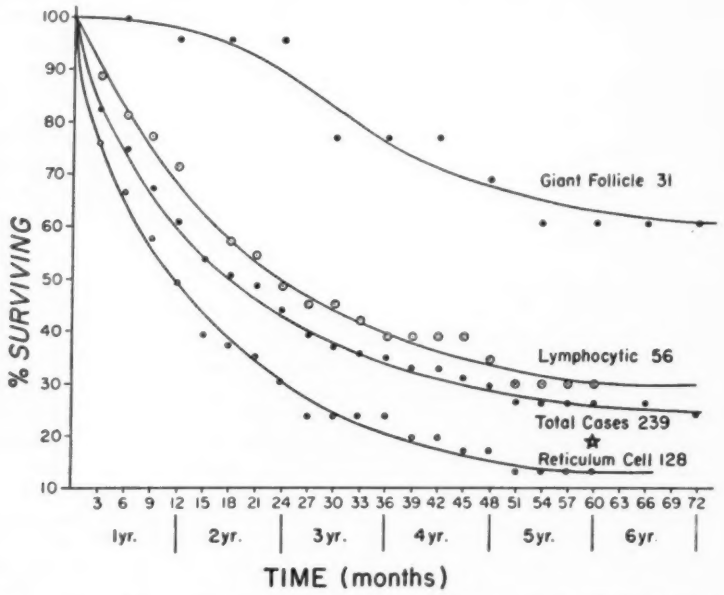


FIG. 1. Survival in lymphosarcoma (published by permission of the publisher [1]).

I have stated that the subclassifications among the lymphosarcomas have clinical significance (figure 1).[1] The giant follicular lymphosarcoma is relatively benign. Characteristically, even bulky adenopathy or massive visceromegaly responds well to radiotherapy, and the remissions are prolonged. Ultimately, however, there are cellular changes, and the course of the disease accelerates with more invasive characteristics. At such time another biopsy will, in the majority of cases, reveal a transition to the reticulum cell type of the disease. The course of the lymphoblastic or reticulum cell lymphosarcoma is, in general, more virulent than the other forms. This may be related in part to the more aggressive invasive qualities of the tumor cells, from which follows frequent destructive involvement of the skeleton, with pathologic fractures, infiltration of the epidural space with phenomena due to compression of the cord, or of the meninges pro-

ducing signs and symptoms of irritation of this membrane, even with depression of the cerebrospinal fluid sugar, which can be distinguished from a bacterial or mycotic meningitis only by appropriate cultures. The gastrointestinal tract and skin are more frequently involved by this form of lymphosarcoma, and it is distinctive in that only in this disease can a terminal explosive invasion of the blood stream occur which has all of the characteristics of acute leukemia.[2]

The lymphocytic or small cell lymphosarcoma is intermediate in its course. In many ways it is closely akin to chronic lymphatic leukemia, even with periodic marked increases in circulating lymphocytes. One interesting phenomenon seen in lymphocytic lymphosarcoma, and only rarely in the others, is a depression of the normal serum gamma globulin. In a recent review of the patients at the

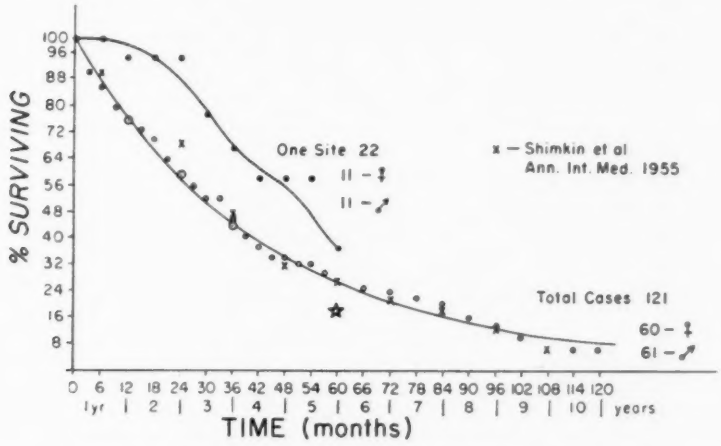


FIG. 2. Survival in Hodgkin's disease (published by permission of the publisher [1]).

Delafield Hospital with lymphoma and significant hypogammaglobulinemia, it was found that over 95% had either chronic lymphatic leukemia or lymphocytic lymphosarcoma, another suggestion of the relationship of these two neoplasms of lymphoid tissue.[3]

To compare and contrast Hodgkin's disease with lymphosarcoma immediately brings to mind certain significant differences. Hodgkin's disease is more common in young adults, with the peak in the second decade falling off to a low incidence from the fourth decade onward. This disease is recognized more frequently at the outset as peripheral adenopathy, and it proceeds with bursts of activity to involve deeper nodes and viscera. The constitutional manifestations of fever, either continuous or remittent, anorexia and asthenia occur earlier, with greater frequency and severity in Hodgkin's disease than in the lymphosarcomas. The total duration of this tumor tends to be shorter. The statistical curves of survival for the lymphosarcomas bring out their general characteristics, as does the similar curve for Hodgkin's disease (figures 1 and 2). Valid as these figures are, when one speaks of groups, it is strongly to be emphasized that there is great individual variation. This makes predictions for

a single case perilous until multiple observations have been made over a period of time, so that the biologic features of the disease in the particular individual are clear.

As to the etiology of the lymphomas, in the past it was assumed that these are malignant neoplasms, and therefore the etiology is unknown. With the interest in the effect of environmental factors in tumorigenesis and the demonstration of their relevance to human cancer, it is no longer permissible to neglect this critical phase of the subject. In the case of the lymphomas, many etiologic factors have been suggested but none has been convincingly demonstrated. For many years, the violent constitutional manifestations so frequently seen in Hodgkin's disease have circumstantially suggested a viral etiology of the tumor. Virology has become an active and productive field of research in the problems of abnormal growth. Dr. Charlotte Friend, of the Sloan-Kettering Institute, will discuss certain aspects of the subject and their relevance to the etiology of the lymphomas.

DR. CHARLOTTE FRIEND: Experimental data which point to the possibility that neoplastic diseases may be caused by viruses have been accumulating since 1908, when Ellermann and Bang discovered that chicken leukemia could be transmitted from one host to another by cell-free preparations. This was followed by the classic work of Rous in 1911 on the cell-free transmission of the chicken sarcoma. Since there are many good articles on virus-induced tumors,[4-7] only a brief review of the subject will be given.

At first it was thought that all types of avian leukosis were caused by one virus, but later, viruses were found which caused only lymphomatosis, myeloblastosis or erythroblastosis. Beard and his group[4] have purified two of these viruses, one of which induces erythroblastic leukemia and the other, myeloblastic leukemia. This last virus is unique in that it contains an enzyme, ATP-ase. Most of the avian leukemia and tumor viruses may be immunologically related.

It seemed that these virus-induced diseases were characteristic of the fowl until the discovery by Shope in 1933 of the papilloma virus of the wild rabbit. This virus causes a benign tumor, a papilloma, in the wild cottontail rabbit, but when it is inoculated into the domestic rabbit, the papillomas almost always proceed to carcinomas. In this same year, Lucké described the virus-induced renal carcinoma of the frog.

Since 1936, when Bittner found that mammary cancer in certain strains of mice was caused by an agent transmitted in the milk to suckling mice, most of the work relating viruses to neoplastic diseases has come from studies on the mouse. There is now a renewed and active interest in the problem, largely due to the impetus given by the rapid advance made in the study of the mouse leukemias.

In 1951 Gross first described the induction of lymphocytic leukemia in newborn mice of specific inbred strains inoculated with cell-free material from leukemic mice of the AK strain mice. After a latent period of several months, a number of these mice developed leukemia and occasionally other tumors. These findings have been confirmed by other investigators, and have lately been extended by Hays et al.[8] and also by Latarjet.[9] Both of these groups report the development of leukemia or tumors in baby mice injected with nucleic acids

prepared from the leukemic organs of AK mice. In studies from the laboratories of both Graffi and Schmidt in Germany, a high percentage of newborn mice inoculated with filtered extracts from various transplantable mouse tumors became leukemic. The acceleration of lymphatic leukemia in AK mice inoculated with filtrates of brain from leukemic AK mice has been reported by Schwartz and Schoolman. These workers have also described two other agents—one

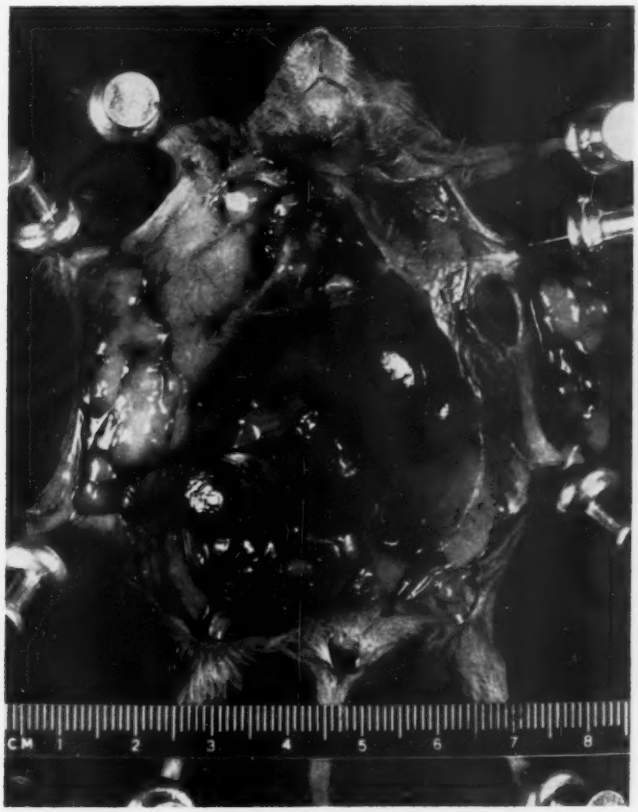


FIG. 3. Evidence of local tumor formation in a DBA/2 mouse after subcutaneous implantation of fragments of leukemic spleen.

which transmits leukemia to Swiss mice, and the other, to C3H mice. Most recently, Stewart and Eddy have succeeded in growing the agent from parotid gland tumors and lymphatic leukemia on mouse embryo cells in tissue culture. The fluid from these cultures induced a remarkable array of tumors when inoculated into infant mice. Some of these virus-induced tumors have never been seen to occur naturally in mice. What is even more startling is that, by passage in tissue culture, the virus loses its species specificity and now causes tumors in hamsters as well as mice.

For the last few years we have been working with an agent which induces leukemia in adult mice.[10] Ultrafiltration and electron microscopic data show that its size is approximately 78 mu.[11] No adaptive procedures are necessary to demonstrate its presence, since from the first, adult Swiss mice were susceptible to infection. The disease which results from the inoculation of the agent is characterized by a short incubation period of about 10 to 14 days, after which massive enlargement of the spleen and liver occurs. Though a few of the mice die within the first three weeks, the majority of them survive for about two months. There are primitive cells in the blood, and mitotic figures are frequently present. Histologic examination of the spleen, liver and marrow from leukemic mice shows massive infiltration with immature cells of the same type.

Since the spleen is strikingly affected, splenectomies were attempted to determine whether the course of the disease would be altered. Spleens were surgically removed from the mice either three days before or three days after inoculation with the agent. In neither case did the absence of the spleen seem

TABLE 1

Neutralization* of the Agent by Specific Antiserum

Serum	Filtrate		Cells	
	No. Pos./ No. Inoc.	% Survivors	No. Pos./ No. Inoc.	% Survivors
Rabbit normal	56/70	20	30/35	14.3
Rabbit immune	5/104	95.2	19/54	65
Mouse normal	20/24	16.7	24/25	4
Mouse immune	3/30	90	10/25	60

* Serum mixture incubated at 37° C. for 1¼ hours before inoculation of 0.2 c.c. intraperitoneally.

to have a therapeutic effect. The survival time of these mice, however, was somewhat longer than that of the intact leukemic controls, which may have died earlier of hemorrhage resulting from rupture of the spleen. The hepatic involvement in the splenectomized mice was more severe than is usually seen. The liver was generally massive and nearly filled the abdominal cavity.

The leukemia agent exhibits a rather narrow range of strain specificity. Six strains of mice have been tested for susceptibility. Other than the Swiss and DBA/2, all were resistant. Serial passages of the agent are being maintained in the DBA/2 as well as the Swiss. The incidence of takes in these inbred mice is consistently 100%, in contrast to a variation between 80 and 100% in the random-bred Swiss. Whereas subcutaneous implantation of fragments of leukemic spleen in Swiss mice caused a generalized leukemia, similar implantation into DBA/2 mice resulted in local tumor formation as well. The tumor-bearing animals (one of which is shown in figure 3) develop a more acute form of the disease, which leads to earlier death. This tumor is being serially transferred and studied for virus content.

The immunologic responses to the agent have also been investigated.[12, 13] The sera of mice and of rabbits immunized with preparations of the agent have been found to contain antibody which neutralizes its infectivity. The results of

some experiments with specific antisera are summarized in table 1. Sera from rabbits before immunization and sera from normal mice served as controls. Only 20% of the mice inoculated with the normal rabbit serum-filtrate mixture survived, in contrast to 95% of those given the antiserum-filtrate mixture. When the cell suspension was tested, neutralization of infectivity was not so great as that seen with the filtrate. Sixty-five per cent of the mice inoculated with the antiserum-cell suspension mixture survived, as compared to 14% of those given cells in normal serum. Antisera from mice gave essentially the same results. Antiserum plus filtrate resulted in 90% survival, whereas with normal sera plus filtrate, the survival rate was only 16.7%. When cells were tested, 60% of the mice survived, as compared to 4% of the controls.

Further indications that neutralization of infectivity is brought about by specific antiviral antibody were obtained from studies with absorbed antiserum. Each sample of antiserum was divided into two aliquots. One was set aside and the other extensively absorbed with dried normal mouse spleen and serum before testing. The absorption procedure did not remove the neutralizing antibody. Such antiserum was as effective as the unabsorbed.

TABLE 2

Effect of Vaccination Against the Leukemia Agent

Challenge Inoculum (IP)	Control		Immunized	
	No. Pos./ No. Inoc.	% Survivors	No. Pos./ No. Inoc.	% Survivors
Filtrate	29/35	17	6/44	86.4
Cells	22/29	22	8/40	80

Attempts to transfer immunity passively have not met with much success, possibly because an insufficient quantity of antiserum was employed. Each animal received 0.2 c.c. of rabbit antiserum per injection. If the antiserum was given on three consecutive days before inoculation with the agent, 50% of the mice survived. The best results were obtained if the antiserum was given three hours before the agent. In this case, 70% of the mice survived. If, however, the immune serum was administered after the inoculation of the agent, only a slight therapeutic effect was noted. Of the mice given the serum as early as one hour after the agent, 40% survived. As the time between the injection of the agent and the serum increased, it was accompanied by a decrease in the number of survivors. When the antiserum was given 24 hours after the agent, there was little difference in the survival rate of these treated animals and the controls. Perhaps greater protection would be afforded by mouse antiserum. This experiment remains to be done.

Far better results were obtained using a formalinized preparation of the agent for active immunization of the mice. Filtrates of leukemic spleens were treated with formalin to inactivate the agent, and the mice were given a series of three inoculations with this material. In one such experiment (table 2) the mice were challenged with either a cell suspension or filtrate of freshly prepared leukemic spleen 14 days after the last injection of the vaccine. Normal mice of

the same age and sex were set aside at the beginning of the experiment and served as controls for the challenge inoculations given the vaccinated group. Of the 44 immunized mice challenged with the filtrate, 86% survived, in contrast to 17% of the nonvaccinated controls. When the immunized mice were challenged with cell suspensions, 80% resisted infection, as compared to 22% among the controls. In a similar experiment, the duration of immunity in the vaccinated mice was investigated. Groups of mice were challenged with cell suspensions of leukemic spleen at 15, 26, 51 or 60 days after the last vaccine injection. It was found that the immunity begins to taper off at about the sixtieth day. If, however, mice are given a booster injection of vaccine at that time, the immunity can be reinforced.

At present we are concerned with biochemical studies of the virus. Studies on the purification and concentration of the agent, and the effect of various enzymes on these preparations, are now under way, so that we may go on to the next task of characterization.

Although the virus tumors have been the source of much material for studies on the basic aspects of both virus-host relationships and the neoplastic process, what have these findings to do with cancer in man? A virus which causes a neoplastic disease in human beings is yet to be found, but mention of possibly related conditions should be made. There are viruses which are known to stimulate nonmalignant cellular proliferation in man. Verruca vulgaris and molluscum contagiosum are two such virus-induced benign growths. In herpes zoster, varicella and trachoma, cellular proliferation is a characteristic of the early lesions.

The knowledge we have gained from the study of virus-induced animal tumors will be of great value in our search for similar agents in the tumors of man. It will not be an easy task, for there are many difficulties that are not ordinarily encountered in the investigation of the typical viral diseases. We know now that genetic and hormonal factors are of importance in demonstrating the presence of the milk agent in mammary cancer of mice. We also know that it is sometimes necessary to condition the host in order to detect the virus. For instance, with the rabbit papilloma, conditioning by treatment of the skin with methylcholanthrene or turpentine before application of the virus greatly increases susceptibility. The age of the test animal may be vital in tumor virus studies. The Rous sarcoma virus gives rise to a fatal hemorrhagic disease in baby chicks in which no tumor cells can be detected, whereas in older chickens the virus induces the typical sarcoma. With the Gross leukemia agent of AK mice, no disease is evident in inoculated adult mice, but when baby mice are given the virus they develop leukemia within several months. Immunologic barriers, the rather narrow range of susceptibility, and the fact that virus may not always be detectable—as in the Rous sarcoma or the Shope papilloma—are but a few of the complicating factors that must be considered.

In spite of the obstacles, there are now many workers engaged in research along these lines, particularly with material obtained from patients with Hodgkin's disease or leukemia.

Bostick [14] has reported that an agent present in cell-free filtrates of the lymph nodes of persons with Hodgkin's disease interferes with the growth of influenza virus in the chick embryo. After several blind passages of similar material

intracerebrally in suckling mice, an agent was recovered which produced a fatal encephalitis. Schwartz and his associates [15] have described the acceleration of leukemia in AK mice which had been inoculated with cell-free filtrates of the brains of persons who died of leukemia. Dmochowski and Grey [16] have made an electronmicroscopic study of the nodes of leukemic patients and have found virus-like particles in them.

In 1956, the fundamental discovery that the nucleic acid prepared from the tobacco mosaic virus possessed infectivity [17, 18] led to similar studies with other viruses, notably the neurotropes. As was mentioned earlier, Latarjet and also Hays et al. have reported that the nucleic acid prepared from the tissues of leukemic AK mice was infective. Most recently, Harel and his group [19] have described the development of tumors in infant mice inoculated with ribonucleic acid extracted from the nodes of leukemic human beings. All of these studies await confirmation.

With so many well documented viral tumors of animals, however, it is conceivable that some of the neoplasms of man may also be of viral origin. Such studies, approached in the light of what we have learned of the pathogenesis of the virus-induced tumors, should be rewarding.

Dr. Gellhorn: In the introductory review of the natural history of the lymphomas, mention was made of the constitutional manifestations associated with these diseases. Time does not permit a full discussion of what is known about the pathophysiologic mechanisms leading to some of these, such as loss of appetite, and informative studies on others, such as fever, are not available. Attention might be directed to the intriguing studies recently reported by Mider and his associates.[20, 21] These investigators suggested that the anorexia associated with a growing tumor may be related to a depletion syndrome. Rats bearing Walker carcinosarcoma 256 and showing a reduced food intake were fed lyophilized tumor tissue and, as a result, rapidly increased their food consumption. These findings may have relevance to an important symptom in patients with neoplastic disease.

There is one manifestation which occurs in every patient with malignant lymphoma during his disease, unless an unrelated problem interrupts the natural history of the tumor, and this is anemia. The mechanisms involved have been widely studied, and interesting information has been produced by research here.

Dr. John E. Ultmann: Although the problem of anemia in lymphoma may not be present at first in all patients, ultimately most patients with lymphoma have some degree of anemia. In some this may be the most life-threatening complication of their disease.

In 1906, Pappenheim studied patients with anemia and various neoplasms and came to the conclusion that in most neoplastic diseases the anemia is due to a crowding out of the normal bone marrow elements by neoplastic tissue. Interestingly enough, the same year Hirschfelt described what he called "leukemische Noxen," leukemic toxins, which he claimed depressed the bone marrow, and he found no evidence for invasion and crowding out of normal bone marrow elements by those of neoplastic disease. It wasn't, however, until 1933 that Jaffe seriously questioned the findings of marrow depression. He found in 21 patients dying of leukemia that there was normal or increased erythroid activity in the

bone marrow. In two, there was a large accumulation of hemosiderin in the Kupffer cells of the liver. He came to the conclusion that, in the absence of erythroid depression and in the presence of hemosiderosis, depression of erythroid activity in the bone marrow seemed unlikely to be the cause of anemia. Since that time, and up to the present, investigators have been trying to elucidate the importance of various factors responsible for anemia of the lymphomas and other neoplastic diseases. With the appearance of more refined methods of studying red cell production and destruction, contributions have been made which lead to a better understanding of the cause of anemia in lymphomas.[22]

For purposes of this presentation, let us examine the various factors responsible for erythroid equilibrium, namely, red cell production and red cell destruction (table 3). Anemia can be the result of decreased red cell formation,

TABLE 3

Anemia of Lymphoma

More Destruction	and	Less Production
Defective erythrocyte		Iron deficiency
Intrinsic		Protein deficiency
Extrinsic		Vitamin B_{12} deficiency
?Vascular defects		Replacement by tumor
External loss		Fibrosis
Internal destruction		Chemotherapy and radiotherapy

or of increased red cell destruction, or both may play a role in the anemia of lymphomas. Let us first turn to erythropoiesis. The simpler procedures which can be used for the study of red cell formation are the reticulocyte count and inspection of bone marrow. In many of our patients with lymphoma and leukemia, we find either a slightly elevated reticulocytosis or no reticulocytosis at all. In some patients, especially those who have a Coombs-positive hemolytic anemia, the reticulocyte count may be more elevated. On inspection of the bone marrow in lymphocytic lymphosarcoma, it is a common finding to see lymphocytosis of the marrow. Nevertheless, even when the marrow is crowded with these cells, one can, on inspection, find adequate erythroid representation, and very frequently erythroid hyperplasia. Study of red cell glycolysis and specific enzymes demonstrates that patients with lymphoma have a younger red cell population than do normal controls.[23, 24] A more quantitative method which has recently come into use in assaying red cell formation is that employing iron-59-globulin. By means of this study, so-called ferrokinetics can be evaluated. In essence, the technic consists of the injection of iron-59-labeled globulin, observing its disappearance from the plasma which gives an index of the iron stores, and then (1) noting the reappearance of labeled red cells, and (2) surface-scanning of the sites of red cell production for radio activity. The former technic makes possible some estimate as to the rate of reappearance of the iron which, in this instance, then represents an erythropoietic index.[25] The latter technic may give some indication of the sites where radioactivity increases the most, and may give a hint of extramedullary erythropoiesis.[26, 27] When all of these studies are analyzed, it becomes apparent that red cell formation is generally not only intact in most lymphoma patients who have anemia, but, in fact, is also increased.

This is not to say that there cannot be a decrease of erythropoiesis in some patients. In a certain number, iron deficiency anemia may occur. This is particularly true when there are areas of gastrointestinal involvement by lymphoma, with sizable loss of blood. It may also be seen following other types of hemorrhage, which can be extensive in patients whose platelets are low. In a small number of patients, the gastrointestinal involvement mimics that of sprue, and there is inadequate absorption of vitamin B_{12} and folic acid. More commonly, when there is an inhibition of erythropoiesis one does find fibrosis of the bone marrow or replacement of some of the bone marrow by tumor. The fibrosis may in part be due to tumor cell invasion with secondary reaction of fibrous tissue, or the fibrosis may in part be due to chemotherapy or radiotherapy given at sometime in the distant past.

Having now examined erythroid formation, let us turn in the second part of our discussion to erythroid destruction. Bilirubinemia, which is so common in congenital hemolytic anemias where there is brisk erythroid destruction, is less important in proving the presence of erythroid destruction for patients with neoplastic disease, such as lymphoma. In most instances the erythroid destruction is more subtle, and the bilirubin level rarely rises above the threshold of liver clearance.[25] A more accurate but more tedious method of measuring erythroid destruction is the determination of total fecal urobilinogen. For this method to be accurate, patients must be placed on a balance study, and the stool specimens collected for long periods. When the amount of fecal urobilinogen is then related to the total quantity of hemoglobin present in the patient, a useful figure can be obtained which will be elevated in those patients who have increased red cell destruction and normal liver function.[27] However, it seems to us that, with simpler and more elegant methods available to measure red cell destruction quantitatively, fecal urobilinogen is an impractical method in most situations.

We should now like to discuss some methods useful for the direct measurement of the life span of the red cells. Ashby in 1919 was the first to use differential agglutination. In this method, a patient is transfused with compatible blood cells which are not like his own and which can be detected by agglutination methods. Ashby came to the conclusion that red cells aged and had a life span of approximately 100 to 120 days. Since then, probably more accurate and simpler technics have been developed. Labeling the subject's own erythrocytes with chromium-51 is probably the method most commonly used today. It has again been found by this method that, in patients who are considered to have no reason for hematologic abnormality, the red cell life span is essentially about 100 days, with the red cell half-life of about 32 days. When patients with lymphoma are studied, whether they are anemic or not, in a large number of them the red cell life span is shortened, and eventually this occurs in all of them.[25] Studies carried out at this Institution have shown that when the blood from such patients is given to normal volunteers, in most instances it survives a normal period of time. On the other hand, blood from volunteers given to patients with lymphoma does not survive a normal period of time. This led to the hypothesis that whatever causes the destruction of the red cells was present in the patient and was not transferable with the blood to a normal volunteer. This factor was called the "hemolytic factor of neoplastic disease." [28] It was then of interest to determine whether the red cells, which are destroyed more rapidly, are destroyed

in the spleen. A study was carried out using Cr^{51}-labeled red cells and employing surface-scanning methods for the sites of red cell destruction. In contrast to patients who have normal red cell life spans, in whom neither the liver nor the spleen is particularly active in red cell destruction, in patients with hemolytic anemia associated with lymphoma, the spleen becomes very radioactive, presumably serving as the site of red cell destruction.[29]

Up to this point, nothing has been said about the Coombs' test. This test is a biologic test in which antibodies to human globulin are produced in rabbits, and the antihuman globulin rabbit serum is then employed in the detection of red cells coated with γ-globulin. It may be of interest to note that most patients with hemolytic anemia of lymphoma do not have a positive Coombs' test.[25] In the others, the presence of a positive Coombs' test is not necessarily correlated with an increased red cell destruction. It is common experience to see a positive Coombs' test persist in patients who no longer have hemolytic anemia. Likewise, as has been demonstrated, it is not uncommon to see patients with brisk hemolytic anemias who have negative Coombs' tests.

The next question which could rightfully be asked is, What are the factors responsible for the increased red cell destruction? Experience has shown that there are very few situations in which one can prove an intrinsic mechanism involving defective erythrocytes. In certain patients with acute leukemia it has been demonstrated that the red cells are damaged to such a degree that, when transfused to normal recipients, they are incapable of surviving a normal life span.[22] More commonly, as we have mentioned before, an extrinsic mechanism is involved. Unfortunately, it is not known what this mechanism is. In those instances where the Coombs' test is positive—and these are rare—one might presume that the abnormal coating with protein is responsible for the defective erythrocyte, but, as we have stated earlier, this is not necessarily the case. Other mechanisms besides defective erythrocytes could be responsible for increased red cell destruction. Vascular defects could lead to external loss of red cells or to internal destruction. When external loss is present, this is, of course, easily detected, but internal destruction is more difficult to detect. Price and Greenfield have recently demonstrated this in animals with tumors. They have observed that, if one quantitated the amount of red cell destruction, one could detect an equal amount of red cell deposition in and around the tumors.[22] Such a situation had not been demonstrated in man to our knowledge. However, on three occasions recently we have been able to study patients who had large abdominal masses. It was noted that when various surfaces were scanned for sites of red cell destruction, they showed a predominance of radioactivity over the masses rather than over the liver and spleen. When these patients were examined at autopsy it was found that they had huge hemorrhagic areas laden with red cells, hemoglobin, hemosiderin and macrophages carrying hemosiderin. The amount of red cells destroyed in these areas was sufficient to account for the anemia found in the patients.[29]

In summary: Anemia is a frequent complication of lymphoma. Erythroid production is usually normal or increased, but not sufficient to balance destruction. Erythroid destruction is moderately or markedly accelerated. The cause of erythroid destruction is not yet known.

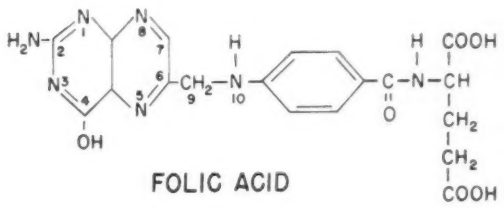
DR. GELLHORN: At the present time there is a national program seeking new antitumor compounds. The selection of potential drugs is made by screening these substances against transplantable tumors in experimental animals. In large part this is an empiric approach, which thus far has had limited success. Far more useful have been studies on the mechanisms of action of antitumor compounds, which have not only explained drug action but have also added knowledge to fundamental cellular chemistry. Dr. Philip Feigelson will discuss this subject.

DR. PHILIP FEIGELSON: There are three motives for interest in the mechanism of action of the carcinostatic compounds. The first is the need of comprehension of the basic biochemical mechanisms which underlie pharmacologic phenomena. The second is the belief that insight into the intimate mechanisms of action of existing chemotherapeutic agents will lead toward the rational development of new and more effective drugs. The third, one of the major clinical difficulties in cancer chemotherapy, as well as a theoretic problem of challenge and import, is the phenomenon of acquired tolerance to carcinostatic agents, whereby a tumor which once responded to treatment by a drug develops resistance and finally becomes insensitive to this drug. It is only through insight into the intimate biochemical mechanisms of drug action that one may approach the study of the alterations in metabolic pathways responsible for the development of such resistance in cancer cells.

Antitumor agents which alter one or more of the vital processes of the tumor cell have been employed both experimentally and clinically. Many of these agents influence either nucleic acid biosynthesis or the function or replication of nucleic acids. During interphase, preceding the initiation of cytologically detectable mitosis, the DNA content of the cell is doubled.[30, 31] Replication of DNA is a necessary prerequisite for the initiation of cell division. Consequently, inhibition of DNA synthesis effectively blocks mitosis, prevents increase in number of cells, and thereby produces carcinostasis. DNA is a polymer of nucleotides, consisting of a purine or pyrimidine base attached to desoxyribose and phosphoric acid. The purines, adenine and guanine, and the pyrimidines, cytosine and thymine, provide the principal heterocyclic bases found in DNA. X-ray crystallographic evidence and studies of these bases of Chargaff[32] led Watson and Crick to the formulation of a model for the DNA molecule.[33] Each molecule is envisioned as a two stranded α-helix with a molecular weight of several million. Each chain consists of a backbone of desoxyribose moieties connected by 3,5 phosphodiester linkages; with the attached purine and pyrimidine bases extending towards the core of the helix. The animal cell is capable of biosynthesizing all of the organic components of this molecule.

The mechanism of action of antitumor drugs will be illustrated with examples taken from purine metabolism, omitting, in the cause of brevity, desoxyribose and pyrimidine biosynthetic pathways. Since the composition of DNA with respect to these bases is characteristic and invariable for each organism, interference with the synthesis of any DNA component would block DNA synthesis and effectively inhibit cell multiplication.

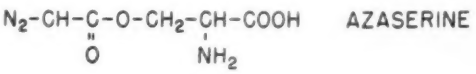
The vitamin, folic acid, is enzymatically converted in vivo to a reduced formylated product, citrovorum factor, and thence to an isomer of this form of folic acid, formyltetrahydrofolic acid (FTHFA).[34–36] The latter participates in

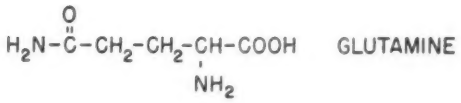


AMINOPTERIN = 4 — AMINO —
AMETHOPTERIN = 4 — AMINO — N^{10} — METHYL —
CF = 5 — FORMYL — 5,6,7,8 TETRAHYDRO —

FIG. 4. The relation of folic acid to its analogs.

the reactions of intermediary metabolism as a one-carbon donor. Aminopterin and amethopterin are structural analogs of folic acid and FTHFA. Aminopterin differs from folic acid by substitution of an amino group for the hydroxyl moiety on the number 4 carbon, whereas amethopterin differs from folic acid by two structural alterations (figure 4). Aminopterin and amethopterin are structural analogs of folic acid which act by competing with folic acid for the enzyme system that reduces folic acid to tetrahydrofolic acid;[37] amethopterin also competitively blocks the utilization of FTHFA.[38] Thus, aminopterin and amethopterin are antimetabolites which effectively induce a reversible deficiency





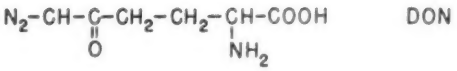


FIG. 5. The structural formulae of glutamine, azaserine and DON.

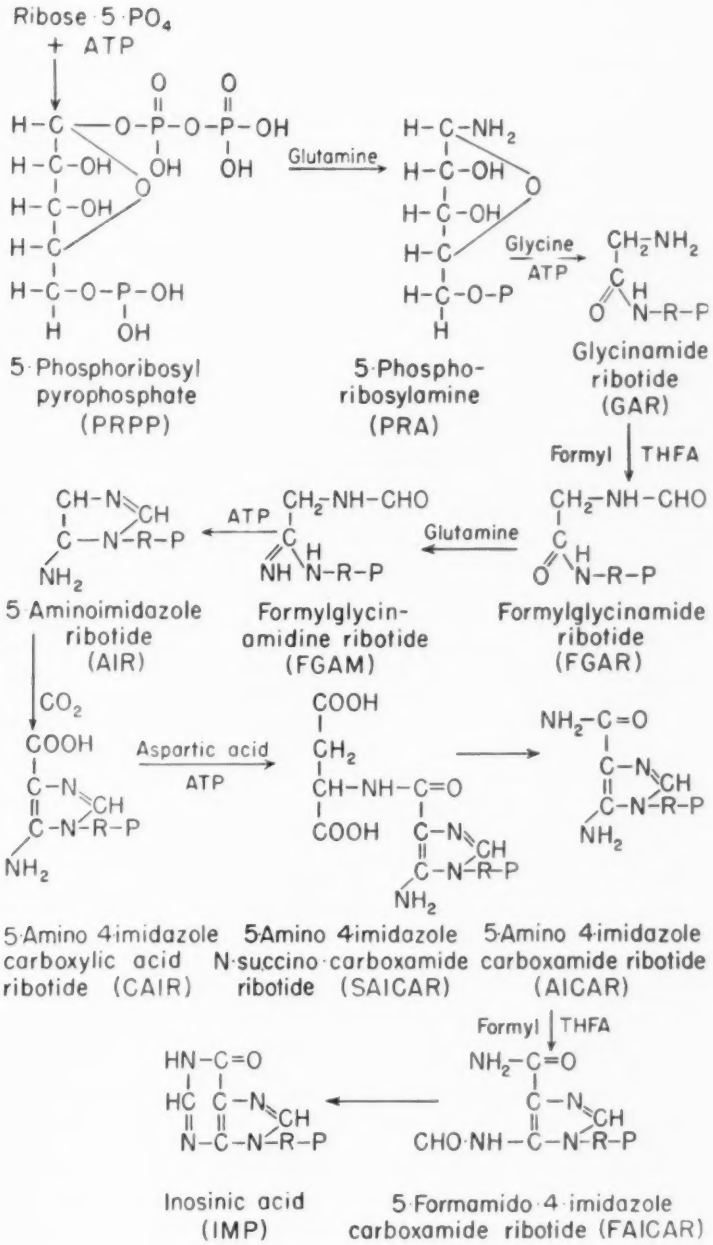


FIG. 6. The biosynthesis of inosinic acid.

in vivo in the active coenzyme form of folic acid, in this way blocking the biosyntheses of compounds requiring single carbon units.

Figure 5 depicts glutamine and the glutamine antagonists, azaserine and diazo norleucine (DON). Glutamine participates in many biosynthetic reactions as a donor of amino groups. Azaserine and DON closely resemble glutamine and therefore compete successfully and, in this instance, irreversibly with glutamine for the active centers of the appropriate enzyme systems. In this way, these drugs interfere with the participation of glutamine in various biochemical reactions in which amino groups are transferred.

The biosynthesis of the purine nucleotides of the nucleic acids illustrates the metabolic lesions induced by these antimetabolites (figure 6). The purine nucleotide, hypoxanthine ribotide (inosinic acid), is constructed by a complex series of reactions in which the component atoms are derived from various precursors.[39] One-carbon fragments carried by FTHFA enter the scheme at two sites; likewise, glutamine transfers its amide nitrogen to the purine ring at two points in this reaction sequence. The folic acid antagonists, aminopterin and amethopterin, serving to diminish the effective levels of the coenzyme form of folic acid, interfere with these one-carbon transfers.[40, 41] The glutamine antagonists, azaserine or DON, block the glutamine donor reactions, resulting in accumulation of formylglycineamide ribotide and inhibition of the biosynthetic pathway.[42] Thus, these agents prevent purine nucleotide biosynthesis which ultimately results in an inhibition of DNA synthesis and cell division.

6-Mercaptopurine (6-MP) is converted in vivo to its nucleotide (6-MP ribotide) by the addition of ribose phosphate to the number 9 nitrogen atom. In this form it is a structural analog of inosinic acid and interferes with the conversion of inosinic to adenylic acid.[43] Since adenylic acid is an obligatory component of the nucleic acids, interference with its biosynthesis results in inhibition of nucleic acid synthesis. Recent studies at the Southern Research Institute indicate that tumors may develop resistance to 6-MP by losing their ability to convert it to 6-MP ribotide, the active inosinic acid antimetabolite. Thus, tolerance to 6-MP seems to be due to a loss by the tumor cell of the ability to convert 6-MP to a pharmacologically active product.

The availability of isotopically labeled purine analogs has permitted detection of the incorporation of trace amounts of certain of these analogs into the nucleic acids, primarily into ribonucleic acid. An alternative hypothesis has therefore been advanced, in which it is the impediment of the metabolic machinery, due to the presence of these abnormal or fraudulent nucleic acids, rather than the interference with nucleic acid biosynthesis which is primarily responsible for the inhibition of cell multiplication.[44]

The mechanism of action of the clinically important mustards and other alkylating agents is less certain. All the alkylating agents possess a common chemical property, namely, the ability to form a carbonium ion.[45] Since the carbonium ion is a carbon atom which lacks one orbital electron, thus carrying a resultant positive charge, it is highly active and reacts rapidly with a wide variety of compounds. There is evidence indicating that mustards react in vivo preferentially with the phosphate moieties of the nucleic acids, and, to a lesser degree, with carboxyl and sulfhydryl groups of proteins.[46] Employing the electron microscope, Stacey [46] has shown structural alterations in DNA fol-

lowing exposure to bifunctional mustards. It is presumed that the resulting distortions in the DNA molecules effected by the mustards prevent mitosis. The demonstration by Zamenhof that the activity of DNA transforming factor is destroyed by exposure to mustards in vitro also provides strong evidence for interaction between these alkylating agents and DNA.[47]

In summary, it may be concluded that the structural analogs of purines inhibit nucleic acid synthesis either by interference with the biosynthesis of necessary intermediaries, or by self-incorporation into nucleic acids yielding nonfunctional, fraudulent nucleic acids. The alkylating agents, however, react with the completed high molecular weight nucleic acids preventing either fulfillment of their physiologic roles or their self-replication, which is inherent in the mitotic process.

DR. GELLHORN: We turn now to the clinical management of patients with malignant lymphomas. The type of treatment and its objectives vary, depending upon the clinical stage of the disease. First, consider apparently localized disease. When this occurs in a peripheral node-bearing site, the most usual situation, it is recommended that aggressive radiotherapy be directed to the area and also to adjacent lymph node regions. For example, involvement of the supraclavicular nodes without demonstrable involvement elsewhere is best treated with tumoricidal doses of radiation to the apparent disease, with additional fields of radiation to the mediastinum. There are skeptics who assert that the lymphomas invariably are multicentric in origin and that there is therefore no justification for such a vigorous radiotherapeutic attack. It is true that many a patient with apparently localized disease shows evidence of widespread involvement distressingly soon after the tumor is first recognized. Since, however, it is impossible to predict the biology of the tumor when it first makes its appearance as an asymptomatic lymphadenopathy, it would seem unwise to take a defeatist attitude and withhold therapy or give it inadequately. The evidence that aggressive radiotherapy to localized disease modifies the natural history rests entirely on the comparison of survival statistics of groups of patients treated when the disease was demonstrably present in only one site, in two sites, or in multiple areas. All clinics are in agreement that those with disease localized to one area have a longer survival. That this may merely reflect the selection of patients with relatively benign or earlier disease cannot be denied, since no series have been reported in which treatment has been withheld from such persons to determine the course of the tumor uncomplicated by therapy. Circumstantial evidence to support the recommendation for aggressive radiotherapy comes from the five- and 10-year survival figures of Peters in Toronto [48] and those of Friedman at the Walter Reed Hospital,[49] who have investigated the prophylactic radiation of adjacent nodal areas. These reporters indicate five-year survival of 60 to 70%, and 10-year survival of about 40%, in the selected group of patients, results well superior to those of others.

What are the special problems when multiple sites are involved, such as peripheral nodes and hepatosplenomegaly? It no longer is appropriate to attempt radiotherapy to each area. This would lead only to undesirable side-effects from radiation, and no useful purpose would be served, since it can be confidently predicted that the disease will make its appearance elsewhere. In the situation just described, if the patient is asymptomatic and has no fever,

anemia or other constitutional manifestations, no therapy is necessary. This occurs reasonably frequently in patients with small cell or giant follicular lymphosarcoma, but is uncommon in patients with Hodgkin's disease or reticulum cell lymphosarcoma. On occasion, at this stage of the disease, one or another site of tumor involvement will produce symptoms due to pressure, which can be controlled readily by radiotherapy.

What of the patient with disseminated disease who is symptomatic? Here, for the first time, serious consideration may be given to the use of drugs. The compounds currently available are particularly valuable in the control of constitutional manifestations such as fever, pruritus and anorexia, and also in decreasing the rate of red cell destruction. In addition, they have a cytolytic action leading to decrease in tumor mass. The most useful compounds are known as the alkylating agents, and their number is legion.

When patients are acutely ill from constitutional manifestations, nitrogen mustard (HN_2, mechlorethamine) is indicated. Smouldering disease can be readily managed on an ambulatory basis by such compounds as chlorambucil or 5-amino-bis-2-chloroethyl uracil. In patients with Hodgkin's disease previously untreated with chemotherapeutic agents, it can be anticipated that 80% will have a remission. Lymphosarcomas respond less regularly and, among these, reticulum cell sarcoma responds least well to drug therapy when it is advanced and producing constitutional signs.

We have emphasized the use of alkylating agents in disseminated disease. There are a few indications for them when lymphomas are localized and are producing pressure on vital structures, such as those within the mediastinum or on the spinal cord. Under these circumstances, it is reasonable to administer HN_2 intravenously to achieve a rapid effect, but when pressure phenomena have decreased or disappeared, full doses of radiation may be given.

The important side-effects of the alkylating agents in man are only two in number. One is stimulation of the vomiting center, an effect which can be controlled with antiemetic drugs. The other is depression of bone marrow function. It is almost invariable that therapeutic benefit is associated with some hematopoietic toxicity. This is reflected in a decrease of all the formed elements. Unless the marrow is already staggering from previous therapy or from the effects of the primary disease, the toxicity is not serious. Adequate time for marrow regeneration should be given before retreatment, that is to say, from four to six weeks.

There is a complication of therapy with alkylating agent which occasionally is of major importance, particularly in the summer. Elevation of the serum uric acid is frequent in patients with lymphomas, presumably a reflection of rapid turnover of nucleic acid. When mustard or one of its congeners is given, there may be prompt dissolution of tumor, with catabolism of purines to uric acid. The uric acid may rise to as high as 22 mg.% and, if an adequate urinary volume is not maintained, urate deposition within the nephron may follow, with obstructive nephropathy.

The antimetabolites have little effect on lymphomas in the adult. In children, in whom the relationship of acute leukemia and lymphosarcoma is often very close, both purine analogs and the folic acid antagonists are useful.

The adrenal cortical steroids are indicated in the management of two general

problems in these diseases. The steroids are frequently very effective in decreasing the increased rate of red blood cell destruction, and they may be necessary for long periods of time. The dosage requirement is usually not above 20 to 30 mg. of prednisone daily. In the natural course of these tumors, it is almost inevitable that major constitutional manifestations will be present at a time when either radiotherapy or chemotherapy with the alkylating agents is contraindicated because of marrow depression. Under these circumstances, prednisone or fluoroprednisone can be expected to control fever, malaise and anorexia, and even to decrease tumor masses. The dosage requirement is high, and the many toxic reactions of these potent hormones must be known and prevented to the greatest extent possible. In addition to disturbances in electrolyte metabolism, production of gastrointestinal ulceration, and exacerbation of latent or mild diabetes, the problem of dissemination of tuberculosis must be remembered. Patients with lymphomas are also more susceptible to mycotic infections, and the lowly monilia, with host defenses lowered by the steroids, may produce a fatal systemic infection. Cryptococci and other pathogenic fungi may also complicate steroid therapy. Because of these many hazards, and because the hormones must be given continuously to control the symptoms, these drugs should be used only when other forms of therapy are ineffective or contraindicated.

Summary

In the setting of the natural course of the malignant lymphomas, we have discussed work in progress of the viral etiology of tumors in animals and the relevance to man; one of the common complications of these diseases, anemia, has been discussed in terms of mechanisms, and mention has been made of other studies which define and clarify pathophysiology of the disease. The mechanism of action of antitumor drugs has been related to nucleic acid biosynthesis and function, and the beginning of insight into the precise mechanisms of drug resistance in tumor cells was discussed. The indications and limitations of therapy with x-ray and drugs were presented, and a reasonable approach to the long-term therapeutic program was outlined.

The manifestations of these diseases can be subtle as well as grossly apparent, and the chronicity and course characterized by exacerbations and often too brief remissions understandably severely strain the morale of the patient and place an increased obligation for understanding on your part. Finally, research is moving these diseases steadily from the realms of mystery and despair toward a position where an increasing number of critical issues may be productively studied.

Summario in Interlingua

Le historia natural del lymphomas es importante ab le puncto de vista del diagnose, del complicationes, e del therapia de iste morbos. Tanto morbo de Hodgkin como etiam le lymphosarcomas pote manifestar se initialmente como localisate allargamentos de nodos lymphatic, con progression del tumores verso nodos peripheric e profunde, visceres, le skeleto, e le systema nervose central. Il ha pauc observationes que indica que le classification histologic de morbo de Hodgkin pote esser correlationate con le characteristicas biologic del tumor. Tamen, in le gruppo lymphosarcomatic, le typo giganto-follicular seque un curso plus benigne e disveloppa sol-

mente verso su termino le characteristicas histologic e clinic de lymphosarcoma reticulo-cellular. Lymphosarcoma lymphocytic o microcellular es intermediari in su proprietates biologic e ha multe aspectos in commun con chronic leucemia lymphatic.

Quando le lymphomas es localisate, le therapia de election es radiotherapia. Quando il pote esser establite que illos se ha disseminate e que illos produce symptomas e manifestationes systemic, le uso de chimotherapia debe esser prendite in consideration. Le disponibile drogas e le indicationes e limitationes de lor uso es presentate.

Il es certo ver que le drogas anti-tumoral es importante in le tractamento clinic del lymphomas, sed illos se ha monstrate de valor ancora plus grande per le information obtenite ab studios del mechanismo de lor action. Tal investigationes ha contribuite al clarification del itinerario biosynthetic del acidos nucleic e ha sublineate le importantia critic de iste constituentes clinic.

Es presentate un revista del importantia de viruses in le genese de tumores, incluse le leucemias e le lymphomas. Le importantia possibile de agentes filtrabile in le causation de lymphomas in humanos es prendite in consideration e le pertinente datos clinic es examinate.

Viste que le lymphomas pote producer multe alterationes in le physiologia del organismo, studios in iste area es importante pro le manipulation clinic de iste problema. Inter tal alterationes, anemia es un del plus commun. Es summarisate observationes que demonstra le importantia del reducite longevitate del erythrocytos in iste morbos.

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CASE REPORTS

NOCARDIOSIS OF THE CENTRAL NERVOUS SYSTEM: REPORT OF TWO FATAL CASES *

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Nocardiosis is a relatively uncommon disease, with only 95 case reports up to 1957 in a comprehensive review by Ballenger.[1] There were 29 reports of involvement of the central nervous system. This report presents two additional cases with central nervous system involvement, one with the gastrointestinal tract as the portal of entry, the other with a pulmonary portal of entry, empyema and sinus tract formation in the chest wall.

Case Reports

Case 1. A 47 year old white male was admitted to Letterman Army Hospital in August, 1956. Three days before admission he had complained of pain but would not reveal its site, and had had one involuntary bowel movement. The following day he was anorectic, restless and lethargic. The third day he complained of headache and was more lethargic, and was admitted to Letterman Army Hospital in an irrational and semicomatose state.

He had been jaundiced in 1951, following a blood transfusion, with resultant chronic hepatitis. Liver function tests had remained abnormal, and repeated liver biopsies were histologically compatible with virus hepatitis and postnecrotic scarring. In 1944 and again in 1947 he had had protracted periods of diarrhea. Since 1950 he had had repeated moderate exacerbations of ulcerative colitis. His diarrhea had been relatively well controlled by 15 mg. of Meticorten daily (prednisone, Schering).

Physical Examination: Temperature, 101° F.; pulse, 100; respiration, 30; blood pressure, 150/65 mm. of Hg. There was icterus of the skin and sclerae and profuse perspiration. There were a few petechiae on the soft palate. The liver was palpable two and one-half fingerbreadths below the right costal margin; it was smooth and slightly tender. The spleen extended two fingerbreadths below the left costal margin. There was nuchal rigidity, with positive Kernig's and Brudzinski's signs. Abdominal reflexes were absent but cremasterics were present. Neurologic examination was otherwise essentially negative.

Laboratory Studies: There was a leukocytosis of 13,600 per cu. mm., with 73% neutrophils, 23% lymphocytes and 4% monocytes. The urine showed 2 plus sugar, and the Watson and foam tests for bile were positive. The urinary sediment contained from 6 to 10 white blood cells, and 2 to 3 red blood cells per high power field. The alkaline phosphatase was 21 SJR units, and the blood urea nitrogen, 22 mg.%.

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The chest x-ray was normal. The spinal fluid had an initial pressure of 330 mm. of water and contained 15,000 white blood cells per cubic millimeter, with 100% neutrophils. The protein content was 330 mg.% and the sugar, 21 mg.%. There were clumps of gram-positive material interpreted as artifacts. Acid-fast stains were negative. A culture of the spinal fluid was negative in 24 hours.

Course in Hospital: Treatment was initiated with sulfadiazine, 30 mg. per pound of body weight intravenously daily, and streptomycin and Chloromycetin, 2 gm. each intramuscularly daily. The lumbar puncture was repeated because of a negative

FIG. 1. Right apical infiltrate and paramediastinal tumor.

spinal fluid culture at 24 hours. The fluid contained gram-positive rods, and an acid-fast stain, with special care to decolorize lightly, revealed filamentous, branching, faintly acid-fast organisms. A tentative diagnosis of nocardiosis was established, and therapy was continued with the addition of cortisone, 100 mg. at once, followed by 40 mg. every six hours. The patient remained febrile, with a temperature up to 104° F. He became completely comatose, developed progressive hypotension, and died 50 hours after admission.

Autopsy Findings: There was splenomegaly with passive congestion, and hepatomegaly with postnecrotic cirrhosis and fine to moderate nodularity. The colon showed the changes of chronic ulcerative colitis without acute ulceration. There

was no evidence of nocardial foci in the lungs. The brain contained multiple abscesses in the left insulotemporal area, one of which had ruptured into the left lateral ventricle, resulting in a meningitis involving the base of the brain, and the brain stem exhibited a pressure cone. A 3.5 cm. ependymoma was found on microscopic examination in the angle between the lateral ventricle and the medial longitudinal fissure, at the level of the basal ganglia. Smears of the exudate from the base of the brain revealed gram-positive, weakly acid-fast filamentous organisms, identified as *Nocardia asteroides*. The organism was nonpathogenic for mice, but caused peritonitis and liver abscesses on intraperitoneal injection into guinea pigs. When grown in litmus milk it was acid-fast, but in guinea pig tissue sections it was nonacid-fast.

Case 2. A 60 year old white female, living in the San Joaquin Valley, in November, 1952, developed progressive hoarseness, fever, and a cough productive of greenish yellow sputum and small amounts of blood. In May, 1953, a chest x-ray revealed a right upper lobe infiltrate and a right upper paramediastinal tumor (figure 1), and she was hospitalized in a local hospital. Bronchoscopy and supraclavicular fat pad biopsy were negative. A coccidioidin skin test was equivocal, but serologic tests for coccidioidomycosis were negative. A thoracotomy in May, 1953, revealed a firm, superior mediastinal mass. A biopsy was reported as showing nonspecific granulation tissue. Tissue cultures were negative, and no acid-fast bacilli or coccidioidal spherules were seen on sections. The patient received 300 units of radiation to the mediastinum, without effect. In June, 1953, incision and drainage of a fluctuant area over the ninth right intercostal space produced pus from which organisms resembling *Actinomyces sp.* were grown. The patient was then afebrile until July, 1953, when her temperature became elevated to 104° F. At this time the eighth and ninth right ribs were resected and the pleural space was explored. No empyema pockets were encountered, and a pleural biopsy revealed nonspecific pleuritis. A fever of 101° F. persisted, and the hemoglobin dropped to 9.9 gm.%, with a leukocytosis of 20,000 cu. mm. There was no response to treatment with 4 gm. of a triple sulfa compound daily. She was transferred to Letterman Army Hospital in August, 1953.

Physical Examination: Temperature, 100° F.; pulse, 84; blood pressure, 134/82 mm. of Hg; weight, 108 pounds (normal, 135 pounds). The patient appeared to be chronically ill, with evidence of recent weight loss. There was an incision over the eighth and ninth ribs posteriorly which was draining dark green, purulent, mucoid-appearing material. There was dullness over the right chest, and breath sounds were decreased with right chest splinting.

Laboratory Studies: There was a leukocytosis of 16,600 per cu. mm. There were 75% neutrophils, 23% lymphocytes and 4% monocytes. The hemoglobin was 10.4 gm.%, and the hematocrit, 36%. The sedimentation rate was 40 mm./hr. The chest x-ray revealed diffuse haziness over the entire right lung field, with infiltration of the right apex. Gastric washings were negative on culture for acid-fast bacilli.

Hospital Course: Treatment was initiated with streptomycin, 1 gm. daily, and isonicotinic acid hydrazide, 300 mg. daily, after obtaining cultures of the pleural drainage and gastric washings. A second strength purified protein derivative (PPD) was positive. By late August, 1953, a fluctuant area had developed over the right chest (figure 2). The right sixth and seventh ribs were resected, and several sinus tracts were entered and the wound was packed. Biopsy of the tissue obtained revealed both acute and chronic inflammatory changes. By mid-September the patient had become confused and lethargic, without localizing neurologic signs. Spinal fluid studies were normal. The exudate from the chest wall obtained in August grew organisms identified as *Nocardia sp.*, which were sensitive to erythromycin and oxytetracycline. Treatment was changed to erythromycin, 1.2 gm.,

oxytetracycline, 2 gm., and sulfadiazine, 4 gm. per day. The patient remained confused, and her steady downhill course continued. Cortisone, 400 mg. per day, was started in early October, with moderate clearing of the sensorium for approximately two weeks. Isonicotinic acid hydrazide was also started again in October. After the transient response to cortisone the patient again became disoriented, then stuporous; she pursued a steady downhill course, and died in December, 1953, 13 months after the onset of her symptoms.

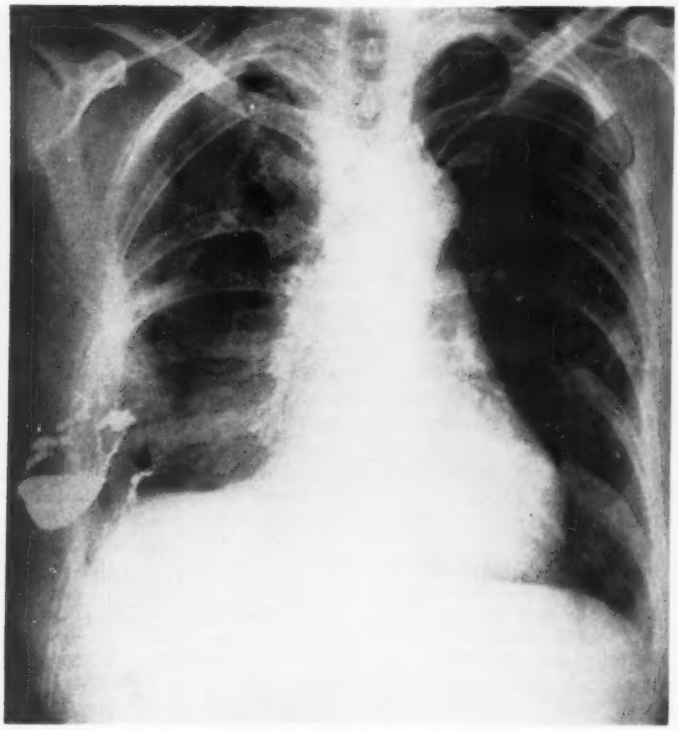

FIG. 2. Sinus tract of right chest wall due to nocardiosis.

Autopsy Findings: At autopsy there were generalized bronchitis and granulomatous pneumonitis involving all lobes. There was a necrotizing lesion of the right adrenal. The brain exhibited a necrotizing meningo-encephalitis with pinhead to pea-sized lesions throughout. Smears of the brain tissue showed mycelia compatible with *Nocardia sp.*, but the organisms were not recovered on culture because of overgrowth of *Proteus*. *Nocardia asteroides* var. *gypsoides* was identified on culture from sputum and from the chest drainage three months prior to death.

DISCUSSION

In a review of 95 cases in the literature, Ballenger [1] found a predominance in males of over 2:1, and ages ranged from four weeks to 70 years. Of 29

cases with involvement of the central nervous system, five survived. Of 66 cases without central nervous system involvement, 16 survived. Of the five cases with central nervous system involvement who recovered, three had excision of the brain abscess,[5, 6, 9] one had ventricular drainage,[4] and one recovered without surgical intervention.[2]

Nocardia asteroides is one of the three pathogenic species of *Nocardia* and is the species usually reported in the United States. It is an aerobic obligate saprophyte, gram-positive, usually weakly acid-fast; it may be bacillary or coccoid, but usually is seen as branching filamentous forms in smears or tissues.[3] It is variably acid-fast, being completely decolorized with the usual staining technics for the tubercle bacillus, and is fragmented or completely destroyed by the concentration methods used for the isolation of the tubercle bacillus.[7, 12] The pitfalls and precautions to be taken in culture and identification have been thoroughly discussed by Wichelhausen.[12] Acid-fastness decreases or may be lost in subcultures or with animal passages.[8] Case 1 illustrates the difficulty of a laboratory diagnosis because of the weak acid-fast staining properties of the organism, and because clumps of mycelia could not be readily distinguished from precipitated particles of stain or other debris.

The respiratory system provides the usual portal of entry, as evidenced by the fact that 67 of the 95 reported cases showed pulmonary involvement. The tonsils, teeth, gastrointestinal tract and skin have all been incriminated as possible entry sites. Breaks in the skin or epithelium would seem to be necessary, as *Nocardia* has no demonstrated power to invade intact skin or mucous membranes.[3] Hickey [3] reported five cases of nocardiosis where there was no evidence of pulmonary involvement, and the gastrointestinal tract was the presumed portal of entry. Case 1 would be included in this category, as no pulmonary lesions could be demonstrated at autopsy, and a chronically diseased colon would have provided ample opportunity for entry. It is notable that there was no evidence of nocardial foci along the route of dissemination from the colon to the central nervous system. No case of spread from the gastrointestinal tract to the central nervous system has been reported.

Nocardial infections are usually chronic and relatively indolent in most tissues. The pathologic picture is one of necrosis with daughter abscesses which show minimal inflammatory response or fibrous reaction, except for secondary scarring. There is little granulation tissue response, and no true granuloma formation. Local extension is by expansion of necrotic areas. Necrosis without surrounding inflammatory reaction is probably the prime factor in the hematogenous spread.[11] The lack of hypersensitivity to *Nocardia* antigen makes skin testing of doubtful aid. McQuown [7] was unable to obtain positive results with a heat-killed vaccine in patients with either nocardiosis or tuberculosis.

Nocardia has been found to be sensitive to a wide range of antibiotics in vitro, but with specific sensitivities varying widely from strain to strain. Culture following antibiotic therapy may be difficult, though abundant organisms may be found at necropsy.[12] Most authors [6, 10, 11] agree that sulfadiazine, alone or in combination with antibiotics, is the treatment of choice. Of the 16 cases surviving with no central nervous system involvement reviewed by Ballenger,[1] nine received sulfonamide compounds, usually sulfadiazine in combination with other antibiotics. Weed in 1955 [11] recommended intensive treatment with

sulfadiazine, 6 to 10 gm. per day. In case 2, however, two antibiotics were used (to both of which the organism was sensitive), in addition to sulfadiazine. In all but one of the reported cases of recovery from central nervous system involvement, there was surgical intervention, either ventricular drainage [4] or excision of the brain abscess.[5, 6, 9] In neither of our cases were localizing signs present to indicate surgery, and necropsy revealed multiple brain abscesses, so that surgical removal would have been impossible. It would appear reasonable to attempt cranial exploration or ventricular drainage in any case of proved or strongly suspected central nervous system nocardiosis if localizing signs are demonstrated.

Summary

Two fatal cases of central nervous system nocardiosis are reported. In case 1 the gastrointestinal tract was the probable portal of entry, but only involvement of the central nervous system was demonstrated. In case 2, both the respiratory and the central nervous systems were involved, and nocardiosis was diagnosed ante mortem. Appropriate therapy was instituted, with no response over a three-month period.

Summario in Interlingua

Es reportate duo casos mortal de infection nocardial del systema nervose central.

In un del casos le diagnose esseva establite per culturas ab un lesion thoracic tres menses ante le morte del patiente. Le uso de antibioticos, seligite super le base de datos de sensibilitate, remaneva sin effecto.

In le altere caso le patiente esseva depost longo affligite de chronic colitis ulcerative. Terminalmente il habeva meningitis fulminante secundari al ruptura de un abscesso cerebral. In iste secunde patiente nulle signo esseva notate de focos de infection nocardial excepte in le systema nervose central.

Inter le previemente reportate casos solmente cinque habeva le vias gastrointestinal como porta de entrata. Le difficultates de establir un diagnose laboratorial de nocardiosis es multiple. Illos resulta primarimente del fragilitate del organismo e del necessitate de prestar grande attention a omne detalios technic pro prevenir le hyperdiscoloration in le tincturation acido-resistente.

Le revista del litteratura indica que infectiones nocardial del systema nervose central ha un prognose multo disfavorabile. Le patiente superviveva in solmente cinque del casos reportate. In quatro de istos, chirurgia esseva requirite.

Es opinate que, in le presentia de signos de localisation in patientes in qui le diagnose de nocardiosis es fortemente suspicite, intervention chirurgic pro objectivos de exploration e drainage o excision in tanto que possibile debe esser prendite in consideration, a parte le therapia con sulfadiazina o antibioticos secundo le indicationes del cultura e del sensibilitates.

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XANTHOMATOUS BILIARY CIRRHOSIS SECONDARY TO CARCINOMA OF THE EXTRAHEPATIC BILE DUCTS *

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WE have found but three reported cases of biliary [3, 4, 5] cirrhosis with generalized xanthomatosis secondary to carcinoma of the biliary tree. Thannhauser and Magendantz in 1938 [1] and Thannhauser in 1940 [2] defined the syndrome as: (1) skin xanthomata of plain and tuberous variety; (2) obstructive type of jaundice of at least one year's duration; (3) enlarged liver and spleen; (4) extremely high values for total cholesterol as well as lecithin; (5) blood serum which was transparent and not creamy, even though the cholesterol was high; (6) low to normal values for neutral fat.

We are reporting an additional case secondary to carcinoma, with the unusual feature of xanthomata in the Achilles tendons bilaterally, as well as widespread plain and tuberous xanthomata.

CASE REPORT

The patient, a 59 year old white female, had been in apparent good health until 1955, when she was hospitalized elsewhere in March because of a complaint of six weeks' duration of deep jaundice, severe itching, nausea, anorexia and diarrhea. The patient had a palpable mass in the right upper quadrant, and a gall-bladder study revealed a nonfunctioning gall-bladder. Blood chemical studies at that time are noted in table 1. The patient was operated upon on March 15, 1955. A chole-

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cystectomy was performed, a "stenotic common-duct" was dilated, and a "T" tube inserted into the duct. No biopsy of the duct was obtained at that time. The final diagnosis was "benign cicatricial stenosis of common-duct, chronic cholecystitis, and choledochostomy."

The patient was left with her "T" tube draining for about a month, and jaundice and other symptoms decreased markedly at this time. The tube was removed and she continued to drain bile through the stab wound. Shortly thereafter she was hospitalized again because of spiking fever and was explored surgically. A fistulous

TABLE 1

Date	Cholesterol Esters	Alkaline Phosphatase B.U.	Lipoproteins B/a+B	Total Fatty Acids	Serum Bilirubin	Phospholipids
Prior to Gall-bladder Surgery						
4/7/55	360/160	43			13.6	
Prior to Exploratory Laparotomy at University Hospital						
2/28/57	1,120	26.1	More than 99%		12.4	2,010
3/5/57	1,392	37.3		1,200	16.4	1,399
3/11/57	1,336			1,016		1,332
Postoperative						
3/25/57		14.4	More than 99%		10.0	
4/1/57		33.7			10.4	
4/4/57	520/185					
4/15/57	305/125	45	More than 99%			
5/24/57	584/406			559		448

biliary sinus tract was excised and a lumbar abscess drained. She was in the hospital for five months (until November, 1955), because her jaundice would intermittently intensify and because of generalized weakness. She was discharged to her home, where her jaundice, although minimal, recurred sporadically.

The patient's condition remained unchanged for nine months, until August, 1956. At that time she first became aware of small yellowish nodules on the palmar surfaces of her hands, elbows and pretibial areas. Her hands especially bothered her, because it became increasingly difficult for her to hold objects—even brushing her teeth was a painful chore.

In January, 1957, the patient went to the University Hospital Dermatology Clinic because of these skin nodules, and in February, 1957, was admitted to the Medical Service of University Hospital. At the time of admission she was cachectic and was deeply jaundiced, with numerous scratch marks. The most notable feature, aside from the icterus and wasting, was the multiplicity of skin and tendon nodules. There were large areas of xanthelasma on both upper eyelids, measuring approximately 1 by 2 cm. in diameter and about 2 mm. in height. The palms of both hands were covered by small, 3 to 5 mm. flat nodules (figure 1). The patient complained of pain in her hands and along both pretibial areas, where there were several tuberous nodules (figure 2). The left Achilles tendon contained some large nodules (about

FIG. 1. Xanthomata of the hands prior to surgery.

FIG. 2. Xanthomata in pretibial areas prior to surgery.

1.5 cm. in diameter). The right Achilles tendon contained some smaller nodules. There were tiny tuberous nodules in both antecubital fossae on both elbows. There were also some tiny tuberous nodules in the skin along the posterior aspect of both ankles. The lungs showed fine crepitant râles at both bases. The heart was small. The liver was at the level of the iliac crest, smooth, firm and very tender; the spleen was felt one fingerbreadth below the left costal margin. Bile was present in the urine, as well as urobilinogen in a concentration of 1 : 10.

Several days after admission the decision was made to explore the patient surgically because of extrahepatic obstruction. At operation a rocklike mass the size of an almond was found in the area of the porta hepatis, surrounding the common duct. A "T" tube was placed in the right hepatic duct, the distal end of

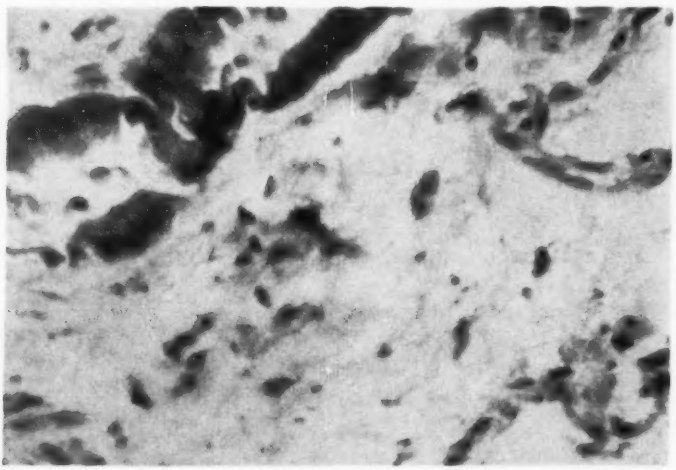

FIG. 3. Biopsy taken from the area of the common duct, demonstrating scirrhous adenocarcinoma.

the tube passing into the duodenum. The patient did extremely well postoperatively. Biopsies of the liver and the mass in the area of the porta hepatis revealed the following.

Pathologic Report: One section from the region of the common bile duct revealed a tumor comprised of irregular, ductlike structures lying widely separated in a dense fibrous stroma. They were lined by cuboidal pyknotic epithelial cells which were fairly uniform in size and form. Scattered about the stroma were small clusters of infiltrating tumor cells (figure 3).

Another section was from the common duct and was generally similar to the first section. Near one edge there was a continuous epithelium, suggestive of the mucosa of the bile duct. Diagnosis: Scirrhous adenocarcinoma of the common bile duct. Obstructive biliary cirrhosis.

The patient's liver chemical test findings began to improve within a week. Neither the protein nor the lipoprotein electrophoretic patterns changed during the hospital stay. At the end of the second postoperative week the patient's jaundice began to decline markedly and the lesions on her hands began to soften. The "T" tube was left in place and was clamped off but irrigated daily. The patient continued to do well and ate splendidly. For a one-week period one month postoperatively she developed clay-colored stools and a rise in serum alkaline phosphatase, but this

reversed itself spontaneously. Her jaundice and skin lesions continued to regress. One of the skin nodules was biopsied and diagnosed as "xanthoma of skin." An intravenous cholangiogram done after the fourth week postoperatively demonstrated apparent malignant infiltration of the distal portion of the common bile duct. There was also evidence of considerable soft tissue neoplastic infiltration in the right upper quadrant.

The partial regression of our patient's lesion was very interesting. The first thing that she noticed was the diminution in pain upon grasping objects with her hands. The nodules on the pretibial areas which had been extraordinarily painful since August, 1956, became painless three weeks postoperatively. No change was noted in the Achilles tendons until about a month after the operation, when a small reduction in size was noted. The patient was discharged and did very well at home until September, 1957. At that time, because of increasing weight loss and weakness, it was necessary to re-admit her to the hospital. Her skin and tendon xanthomata had decreased but she was quite jaundiced. She continued to go downhill over a period of two months, and died on November 3, 1957, almost three years after she had first become jaundiced.

The autopsy revealed extensive recurrent tumor obstructing the bile ducts. There was an obstructive biliary cirrhosis of moderate degree. The only remaining manifestation of xanthomatosis was the presence of numerous foam cells in the vertebral marrow and in the hepatic sinusoids.

Discussion

In this case of adenocarcinoma of the extrahepatic bile ducts generalized xanthomatosis developed due to the extended survival of the patient, and the presence of a constant marked hypercholesterolemia. The lesions in the Achilles tendons were not apparent at autopsy, nor were the skin lesions. It is felt that the lowering of the cholesterol caused by the free passage of bile to the intestine was the sole factor involved in their disappearance.

The earliest reported case of xanthomatosis in which biliary cirrhosis had been caused by a carcinoma of the biliary tree was reported by Pye-Smith in 1877.[3] This was a 57 year old sailor who had suffered for six weeks with jaundice, pruritus and slow pulse, and subsequently was admitted to Guy's Hospital. There he had facial erysipelas and, subsequent to this, developed xanthelasma of the lower eyelids. This was the extent of his xanthomatosis. At necropsy, six weeks later, a carcinomatous tumor at the junction of the pancreatic and common ducts was described. The next case was reported by Weidman and Boston,[4] a case of xanthoma tuberosum secondary to an obstructive duct carcinoma. Syphilis of the liver was also present, however. In their case there was generalized xanthoma tuberosum with xanthomatous changes in the fresh scars of an intercurrent herpes zoster. They thought that an adenomatous polyp at the duodenal papilla was the beginning of the entire disease complex, and that malignant changes had developed in the polyp at a comparatively late date. Ahrens et al.[5] mention, via personal communication, a case of Klatskin's where there was an adenocarcinoma at the hepatic duct junction in a 26 year old male in whom there was generalized xanthomatosis.

No mention was made in any of the reports as to whether tendon lesions were present. The presence of tendon lesions in our case would tend to support the view that their presence in any part of the body is merely a function of elevated cholesterol and time, and not anything more specific.

SUMMARIO IN INTERLINGUA

Nos ha trovate solmente tres reportate casos de cirrhosis biliari con xanthomatosis generalisate secundari a carcinoma del arbore biliari. Es presentate un caso additional secundari a carcinoma, con le tracto inusual de xanthomas in le tendines de Achilles a ambe lateres e le presentia extense de xanthomas ordinari e tuberose.

Le patiente esseva un femina de 59 annos de etate. Illa habeva essite subjicite a cholecystectomia pro jalnessa obstructive, sin exploration del ducto commun. Subsequentemente illa disveloppava xanthomatose cirrhosis biliari con xanthomas de tendine (in le tendines de Achilles). Re-exploration resultava in le constatation que le syndrome esseva causate per un adenocarcinoma scirrhose, primarimente situate in le ducto commun. Un tubo plastic in forma de T esseva inserite. Le lesiones del patiente, su hypercholesterolemia e su jalnessa subsideva rapidemente, e ille viveva ancora un anno.

Le morte occurreva tres annos post le declaration de symptomas. Le causa de morte esseva carcinoma. Le valores pro lipido total ante le secunde operation variava inter 2,5 e 5,0 g pro cento. Iste alte nivellos habeva persistite durante al minus un anno.

Nulle previe reporto que nos ha incontrate in nostre revista mentiona specificamente le presentia de lesiones in tendines. Le presentia de lesiones in tendines in nostre caso supporta le opinion que le occurrentia de ille lesiones in non importa qual parte del corpore es simplemente un function del elevate nivellos de cholesterol e del tempore e non un phenomeno de causation plus specific (como per exemplo hereditage).

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TRACHEOPATHIA OSTEOPLASTICA *

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TRACHEOPATHIA osteoplastica is a relatively rare disease involving the trachea and bronchi. Slightly over 100 cases have been reported in the world

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literature to date since the disease was first described in 1857 by Wilks [1] in England. Since 1932 only 11 cases have been reported in the American literature, the latest report being an account of seven cases diagnosed at the Mayo Clinic.[2]

Case Report

A 63 year old white male was admitted to the U. S. Public Health Service Hospital, Norfolk, Virginia, on August 15, 1956, with the chief complaint of hemoptysis of four days' duration. The patient stated that he had had mild "bronchial asthma" for 15 years, aggravated by upper respiratory infections. On several occasions in the past he had experienced hemoptysis. Shortly before admission he had developed a cough, malaise, fever, left pleuritic chest pain and mild exertional dyspnea. There was no history of weight loss or night sweats. Approximately one month prior to admission the patient's daughter had died of pulmonary tuberculosis; the patient had nursed his daughter during this illness. The remaining portions of the past history and systems review were noncontributory.

Physical Examination: Blood pressure, 130/64 mm. of Hg; pulse, 84/minute; temperature, 101.3° F.; respirations, 24/minute. The positive physical findings were limited to the chest. The trachea was in the midline. Inspiratory and expiratory coarse rhonchi were audible throughout both lung fields, with a prolongation of the expiratory phase. There was an increase in the anteroposterior diameter of the chest, and the intensity of the breath sounds was somewhat diminished throughout both lung fields. No areas of dullness to percussion or changes in vocal or tactile fremitus were evident. The heart had a normal sinus rhythm and was not enlarged to percussion. A Grade II pulmonic systolic murmur was transmitted over the entire precordium; however, it was not transmitted into the neck. P_2 was of good quality. A_2 was greater than P_2. The rest of the examination was within normal limits.

Laboratory Studies: A serologic test for syphilis was nonreactive. A hemogram showed a white blood count of 16,400, with 73% neutrophils, 25% lymphocytes, 1% monocytes and 1% eosinophils. Hemoglobin was 14.5 gm., and hematocrit 49% and sedimentation rate 25 mm./hour. Urinalysis results were within normal limits. Sputum culture revealed the presence of alpha streptococci and nonhemolytic *Staphylococcus albus*. Sputum smears and cultures for acid-fast bacilli were negative, as were sputum cultures for fungi. X-ray of the chest on August 16, 1956 (figure 1), revealed an area of infiltration involving the entire midportion of the left lung field and extending upward from the hilum into the second left anterior interspace, with an area of radiolucency just to the left of the cardiac silhouette. A mottled area of nodular density was seen in the periphery of the left lung, which was interpreted as either an emphysematous bleb or a possible cavity.

Hospital Course: The patient manifested a septic-type febrile pattern during the first 10 days of hospitalization, which responded by lysis to tetracycline therapy. Repeat chest x-ray on August 30, 1956, revealed considerable clearing of the infiltrative process involving the left lung field; however, much residual still remained, extending peripherally from the left hilum. Several small areas of radiolucency were present, but no definite or distinct area of cavitation was seen. A first strength tuberculin test was strongly positive. The histoplasmin skin test was positive in 24 hours; the coccidioidin and blastomycin skin tests were negative. On September 5, 1956, bronchoscopy was performed; the larynx appeared to be normal, and the carina was slightly widened; the trachea and right bronchial tree appeared to be normal. However, when the left main-stem bronchus was entered, a mass was observed protruding from the medial anterior wall just opposite the left upper lobe bronchus.

which was still patent. Eight biopsies were taken from this area, and the microscopic examination of these biopsies showed the surface epithelium to be normal in appearance. The basement membrane appeared to be slightly thickened. The mucous glands and the underlying cartilage were without remarkable changes. Scattered through the connecting stroma was a homogeneous, somewhat hyaline material with an occasional foreign body giant cell. Similar material was seen within the smooth muscle tissue. One of the hyaline-appearing areas stained somewhat basophilic and contained a small amount of calcium. These findings were interpreted as possibly

FIG. 1. X-ray of the chest on August 16, 1956, reveals an area of infiltration involving the entire midportion of the left lung field and extending upward from the hilum into the left second anterior interspace, with an area of radiolucency just to the left of the cardiac silhouette. A mottled area of nodular density is seen in the periphery of the left lung, which is interpreted as either an emphysematous bleb or possible cavitation.

representing primary amyloidosis. Amyloid stains, however, were unsatisfactory for positive interpretation. Acid-fast cultures, fungus cultures and cytologic studies of the bronchial washings, obtained at the time of bronchoscopy, were all negative. On September 20, 1956, a left scalene node was obtained, and the pathologic sections were negative for tumor and negative for a specific inflammatory process. On October 2, 1956, an x-ray of the chest showed that there had been an increase in the density involving the left lung field. There were also blunting of the left costophrenic angle and elevation of the left diaphragm, which had not previously been present. In the midportion of the density of the left lung field a rounded density was seen which

had increased considerably in size since the examination of August 30, 1956. A left lateral x-ray of the chest on October 5, 1956, revealed the infiltrative process involving the left lung field to be situated in the region of the hilum, lingula and anterior segment of the left upper lobe. The posterior angles were blunted.

During this period the patient's weight remained stationary at 160 pounds, which was his average weight. In view of the negative findings during the medical studies, the case was reviewed at Chest Conference and it was decided that thoracotomy was indicated. The patient was placed on isoniazid, 100 mg. three times daily, and para-aminosalicylic acid, 4 gm. three times daily for two weeks preoperatively. On

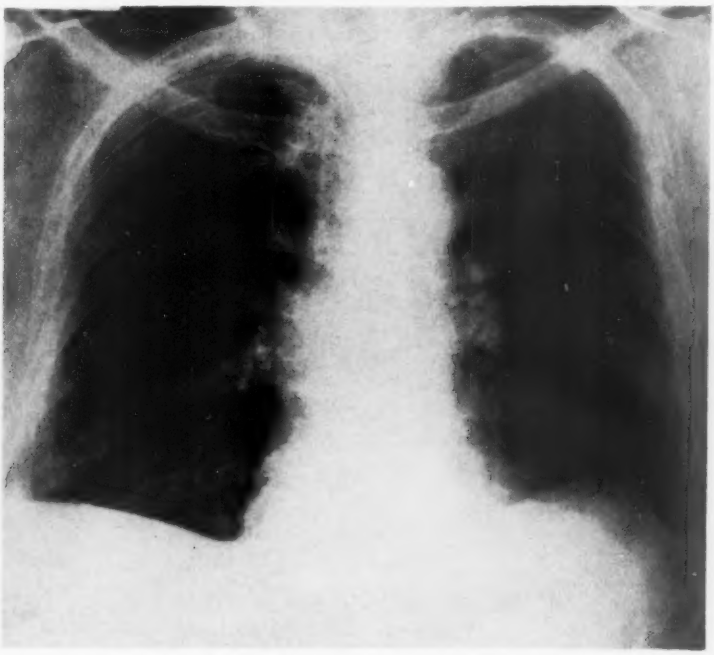

FIG. 2. X-ray of the chest on April 15, 1957, shows marked clearing of the process involving the left lung field and the left hilar regions; the marked atelectatic process involving the left lower lung field has shown remarkable clearing.

November 16, 1956, an exploratory thoracotomy was performed under endotracheal ether anesthesia. The mass in the left hilum was found to be located just below the left pulmonary artery, and seemed to include the left main stem bronchus just below this artery. A large solitary hilar lymph node was removed for pathologic study. It appeared that the pericardium was closely involved in this process. The clinical impression at the time of surgery was inoperable bronchogenic carcinoma, and the chest was closed. The lymph node removed at the time of thoracotomy revealed only anthracotic change. Some pleural fluid removed at the time of thoracotomy showed cells which were reported as highly suggestive of malignancy. Following the postoperative period the patient requested permission to visit his family in the southwestern section of the United States, and remained there through the winter of 1956–1957.

The patient was again seen as an outpatient on April 15, 1957, at which time he had no specific complaints except for vague left chest wall pain in the area of the previous thoracotomy incision. He had had no hemoptysis or cough, and had remained asymptomatic throughout the winter. Examination of the lungs at that time revealed some decrease in the audibility of breath sounds over the left upper lung, but no râles were heard. X-ray of the chest on April 15, 1957 (figure 2), showed marked clearing of the process involving the left lung field and the left hilar region; the markedly atelectatic process involving the left lower lung field had shown remarkable clearing. The patient remained asymptomatic until September 23, 1957,

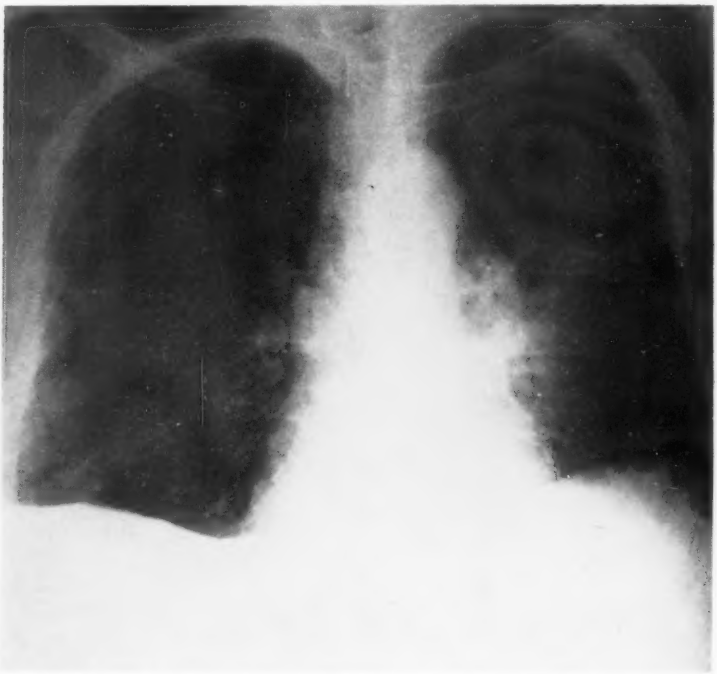

FIG. 3. X-ray of the chest on October 14, 1957, reveals an increase in the extent of the process involving the left midlung field, as compared with the previous x-ray. Changes in the left hilum and the tenting of the left diaphragm are again seen. It is felt that these changes are consistent with an inflammatory process.

when he developed a cough productive of whitish sputum with some hemoptysis. X-ray of the chest on September 23, 1957, showed no significant change from the x-ray taken on April 15, 1957. During this period the patient's weight had remained stationary at 160 pounds. He was seen again in the Medical Outpatient Department on October 14, 1957, complaining of pleuritic left chest pain, with some increased cough productive of mucoid sputum. He had a temperature of 102° F. orally. He was re-admitted to the hospital on October 14, 1957. An x-ray of the chest at that time (figure 3) revealed an increase in the extent of the process involving the left midlung field as compared to the film of September 23, 1957. The changes in the left hilum and the tenting of the left diaphragm were again seen. It was felt that these

changes were consistent with an inflammatory process. A white blood count showed 18,650 white blood cells, with 64% neutrophils, 2% stabs and 34% lymphocytes. The hemoglobin was 16 gm.; hematocrit, 51; sedimentation rate, 16 mm./hour. Sputum culture failed to reveal a predominant organism. The patient ran a septic-type temperature curve for the first two weeks of hospitalization in spite of penicillin, 600,000 units twice daily. On November 5, 1957, bronchoscopy was again performed. The trachea was normal and the carina was in the midline. The left upper lobe orifice was examined and was quite edematous but patent. Just opposite this orifice there was a smooth, soft mass with hyperemic mucosa. It did not bleed until pressure was applied to the area. The mass completely obstructed the main stem bronchus, beginning 3 cm. below the carina. Biopsies taken from five areas of this mass on

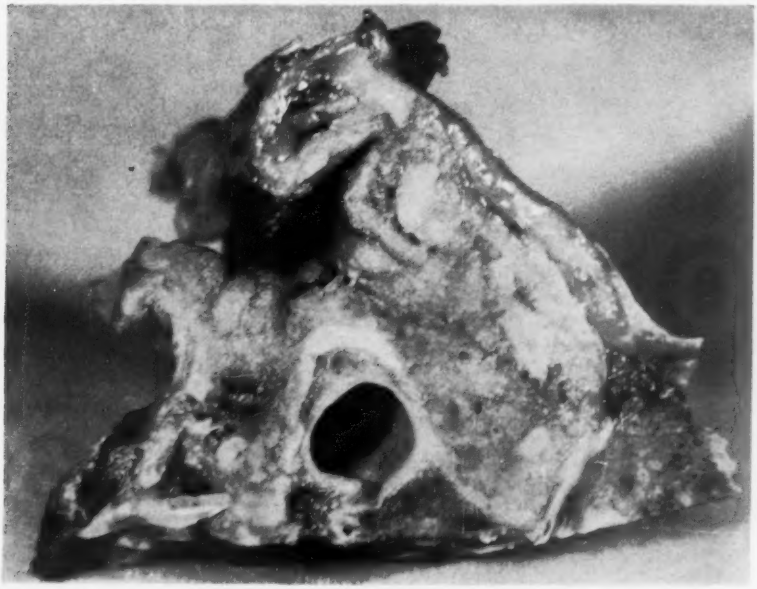

FIG. 4. Cut section of the left lung following removal. The left lung weighs 375 gm. The open bronchial tree shows an irregular thickening of the bronchial wall, with partial stenosis of the peripheral orifices of the left main stem bronchus.

microscopic section showed fragments of respiratory mucosa, with a mild lymphocytic infiltration and a tendency of the columnar epithelium to undergo squamous metaplasia. Edema, clusters of active mucosal glands, nonspecific degeneration of cartilage and focal areas showing thickening of the basement membrane were also noted. There was no evidence of malignancy. The acidophilic thickening of the basement membrane once again suggested the possibility of amyloidosis. In some areas the cartilage exhibited calcification, fragmentation and necrosis. A crystal violet stain of the specimen showed the acidophilic material to be chemically similar to amyloid.

In view of the findings at the time of thoracotomy, the later course of improvement, both clinically and on x-ray examination, and repeatedly negative findings as to malignant growth, the patient was again presented at Chest Conference. It was decided that, in view of the repeated infections in the left lung and the findings on

bronchoscopy of nearly complete occlusion of the left main stem bronchus, it was justified to attempt to remove the lesion surgically. On November 19, 1957, under endotracheal ether anesthesia, a left thoracotomy was performed. A marked inflammatory reaction and fibrosis were found encroaching upon the left hilum, so that extrapericardial ligation of the pulmonary vessels was not possible. This necessitated the intrapericardial approach to these vessels; however, during the operative procedure a perforation was inadvertently made in the left pulmonary artery, and the patient died before the bleeding could be controlled.

Autopsy Findings: Examination of the lung (figure 4) showed that it weighed 375 gm. When the bronchial tree was opened there was an irregular thickening of the bronchial wall, with partial stenosis of the peripheral orifices of the left main-stem bronchus. The tissue cut with a slight increase in resistance. The cartilage plates had a granular texture and, when sectioned, were ragged, and varied in color from yellow to light gray. Microscopic examination of the walls of the bronchial tree showed them to be markedly thickened, due to the presence of multiple cartilaginous and bony growths. Many of these showed no apparent connection with the preëxisting cartilage plates. Between and around the new bone spicules were foci of marrow containing megakaryocytes. The preëxisting cartilage rings exhibited degenerative changes, bony metaplasia, and an irregular proliferation of perichondrial elements. The intervening soft tissue manifested such changes as necrosis, foreign body giant cell activity, fibrosis, old hemorrhage, thickening of the basement membrane of mucosal glands, and a variable mononuclear inflammatory infiltrate. The adjacent and distal pulmonary parenchyma displayed septal fibrosis, partial atelectasis, numerous intra-alveolar pigmented macrophages with erythrocytes, fibrotic thickening of vessel walls, precipitated fluid, and an intense mononuclear inflammatory infiltrate, both focal and diffuse. The walls of the involved bronchial tree were also heavily infiltrated with mononuclear cells and, in some instances, the respiratory mucosal elements were rather hyperplastic. No evidence of malignancy was found. These findings were considered to be diagnostic of tracheopathia osteoplastica, and the diagnosis was confirmed by the Armed Forces Institute of Pathology.

Comment

Tracheopathia osteoplastica is characterized by osseous and cartilaginous growths occurring between the tracheal and bronchial rings. It has been reported [3] that the process is more likely to occur between the ages of 30 and 60, with no sex predominance. This process is usually limited to the lower two thirds of the trachea. The posterior membranous portion of the trachea is spared. The process may spread from the trachea to involve the main-stem bronchi. Grossly, the lesions appear as small, hard nodules under a normal appearing mucosa, situated between the cartilaginous rings of the trachea and the main bronchi. These nodules may coalesce to produce a diffuse thickening or large, plaquelike areas.

Microscopically, one sees elastic cartilage in different phases of development, associated with calcified cartilage, osteoid tissue and typical marrow-containing bone.

The exact origin of these osteoma-like growths is not known, but at the present time Carr and Olsen [2] believe that the theory of Dalgaard [3] is the most acceptable. According to this, elastic connective tissue cells in the wall of the trachea develop into cartilage cells through direct metaplasia. These grow into islands of cartilage, which become partially calcified. The islands are invaded by connective tissue that is rich in blood vessels, resulting in the forma-

tion of marrow cavities lined by osteoblasts, which may account for the transformation into bone.

Clinically, the symptoms may consist of gradually increasing dyspnea, hoarseness, cough, expectoration and hemoptysis. The severity of the symptoms depends upon the extent of the lesions and the degree of tracheal or bronchial obstruction present. This lesion may even mimic bronchogenic carcinoma, as reported by Flick [4] and Lell.[5]

The diagnosis of tracheopathia osteoplastica is made primarily by bronchoscopy. There is marked rigidity of the trachea and bronchi. In early cases the tracheal and bronchial walls may present a beaded appearance, due to the presence of many nodules. As the disease progresses the nodules may coalesce and form polypoid lesions or large, plaquelike areas. These lesions are invariably covered by an intact mucosa. Tomograms may be useful in diagnosis. The tomograms may depict thickening of the entire tracheal and bronchial wall, the surface of which has a beaded or scalloped appearance, produced by the coalescence of the calcified nodules. They may also show narrowing of the airway.

The course of the disease is variable. The degree of obstruction of the airway and the presence or absence of obstructive pneumonitis are of greatest importance in determining the outcome in any given case. There is no known specific treatment; however, Jackson and Jackson [6] report one case treated with x-ray therapy, with apparently good short-term results in controlling hemoptysis.

Summary

A case has been presented of tracheopathia osteoplastica, characterized by involvement limited to a left main-stem bronchus, without evidence of tracheal change. The authors believe that this is the first recorded case with this unique distribution of the disease process. A brief review of tracheopathia osteoplastica is included with this report.

Summario in Interlingua

Tracheopathia osteoplastic es un morbo relativemente rar que affice le trachea e le bronchos. Pauco plus que 100 casos se trova reportate in le litteratura mundial. Le caso hic presentate es illo de un masculo de racia blanc de 63 annos de etate con le gravamine de hemoptysis. Le roentgenographia del thorace revelava un area de infiltration que comprendeva le integre portion central del campo pulmonar sinistre. Bronchoscopia revelava un lesion que protrudeva ab le sinistre broncho intra-pulmonar. Biopsias non esseva diagnostic. Un thoracotomia exploratori monstrava que le massa involveva le hilo sinistre. Le lesion esseva reguardate como un carcinoma inoperabile. Un grande solitari nodo lymphatic esseva excidite sed monstrava solmente alterationes anthracotic. Le patiente esseva dimittite. Ille retornava cinque menses plus tarde pro un examine de controlo. Durante le intervallo ille habeva remanite asymptomatic. Un roentgenogramma del thorace monstrava un marcate clarification del processo afficiente le campo pulmonar sinistre. De novo omne le studios esseva negative, con le exception del bronchoscopia que de novo monstrava le massa involvente le sinistre broncho intra-pulmonar. Biopsias revelava alterationes de character non-specific. Post ancora un episodio de pneumonitis sever, un secunde thoracotomia esseva effectuate. Marcate grados de un reaction inflammatori e de fibrosis esseva evidente circum le hilo sinistre. Durante le effectuation de un pneumonectomia, le arteria sinistro-pulmonar esseva perforate per

inadvertentia, e le patiente moriva ante que il esseva possibile arrestar le sanguination. Le examine del pulmon revelava alterationes characteristic de tracheopathia osteoplastic.

Tracheopathia osteoplastic es characterisate per crescentias ossee e cartilaginose que occurre inter le anulos tracheal e bronchial. Usualmente illo es locate in le duo tertios inferior del trachea. Le portion membranose posterior del trachea remane exempte. Le processo pote extender se ab le trachea e afficer le bronchos intrapulmonar. Le diagnose es usualmente facite super le base del constatation bronchoscopic de micre nodulos dur sub un mucosa de apparentia normal. Le examine microscopic monstra cartilagine elastic in varie phases de disveloppamento, in association con cartilagine calcificate, tissu osteoide, e osso typic a contento medullar. Le causa le plus probabile de iste crescentias de character osteomoide es que le cellulas de elastic tissu conjunctive in le pariete del trachea se disveloppa in cellulas de cartilagine per un processo de metaplasia directe.

Clinicamente, le symptomas pote consister de un augmento gradual de dyspnea, raucitate del voce, tusse, expectoration, e hemoptysis. Le severitate del symptomas depende del extension del lesiones e del grado del obstruction tracheal o bronchial. Le lesion pote simular carcinoma bronchogene multo proximemente. Tomogrammas es possibilemente de valor in le diagnose de iste lesion.

Le grado de obstruction del vias aeree e le presentia de pneumonitis obstructive es del plus grande importantia in determinar le ultime resultato del caso individual. Il non existe un therapia satisfacente. Il pare que le presente caso es le prime unquam reportate in que le processo pathologic esseva restringite al sinistre broncho intra-pulmonar sin ulle signo de un affection del trachea.

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CHRONIC NEUTROPENIA IN SIBLINGS: THE EFFECT OF STEROIDS*

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THE literature is replete with articles on the use of steroids in the treatment of drug-induced agranulocytosis but not with articles on nondrug-induced, non-

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cyclic, nonsplenic neutropenia. Two cases of the latter type in siblings are presented, in the second of whom a favorable response to steroid therapy was obtained.

The mother of these children has a duodenal ulcer and disseminated lupus erythematosus, currently controlled with the use of prednisone. Her blood count and peripheral blood picture have always been normal. Examination of her bone marrow revealed numerous L.E. cells of the Hargraves' type. The children's father had had a coronary thrombosis at the age of 46, from which he recovered. Their brother died at the age of 15 of bronchopneumonia secondary to measles, prior to the availability of the antibiotics.

Case Reports

Case 1. A girl born in Oregon in 1933 had always been fairly well, except for an attack of chickenpox, until the age of five, when she began to have frequent infections of the upper respiratory tract, for which sulfonamides were administered. In February, 1941, while living in the vicinity of San Francisco, she had an acute illness characterized at onset by abdominal pain and fever, and an occasional mild cough with râles at the bases of both lungs. Severe gingivostomatitis and ulcerating lesions of the right leg and the right side of the scalp developed. Her total neutrophil count varied from zero to 200. The neutropenia persisted with fluctuations during this illness. There was no history of ingestion of coal-tar derivatives. Bone marrow obtained by sternal puncture March 23, 1941, was described as follows: "The maturation of granulocytes appears partially arrested at the myelocyte level." Multiple transfusions of blood were given, following which hepatomegaly and jaundice developed. Injections of yellow bone marrow extract, liver "cocktails," Reticulogen and Pentnucleotide were of no benefit. The ulcerations were treated by local applications and ultraviolet light, with slow improvement. The diagnosis at that time was idiopathic familial neutropenia.

On June 12, 1941, at the age of eight, the patient was hospitalized. Physical observations included an extensive superficial ulceration behind her right ear, a small pustule on the left forearm, and an extensive, ulcerating lesion on the right leg. The liver was palpable one to two fingerbreadths below the right costal margin. The erythrocyte count was 4,600,000, with 12.5 gm. (84%) hemoglobin. The leukocyte count was 11,600, with 21% neutrophils, of which 14% were metamyelocytes, 50% lymphocytes, 24% monocytes, 1% eosinophils and 4% basophils. The urine was normal.

On June 18, because of the chronic course of the disease and the patient's failure to improve, a splenectomy was done. Pathologic examination revealed severe congestion and hemosiderosis of the spleen. Following the splenectomy the leukocyte count averaged 12,000, with 10% neutrophils, of which about half were metamyelocytes; basophils varied from 1 to 10%; platelets varied from 500,000 to 2,000,000, and reticulocytes from 0.5 to 2.0%. There were usually 10 to 40% smudge cells. With increase in the leukocyte count there was complete clearing of the gingivitis, and the ulcerating lesions behind the right ear gradually disappeared. The ulcer of the right leg healed slowly and irregularly, but large granulating areas were still present at the time the patient left the hospital. A complete roentgenographic study of the bones revealed changes in the calvarium and right ilium suggestive of those characteristics noted early in erythroblastic anemia. In view of the finding of achlorhydria on gastric analysis, a trial period of therapy with hydrochloric acid drops was instituted, followed by a moderate improvement in the blood picture. This good result, however, was short-lived, and the hydrochloric acid was discon-

tinued. The total neutrophil count during this period varied from 500 to 2,000. The discharge diagnosis was neutropenia of unknown cause.

In May, 1942, while living in Georgia, the patient, now aged nine, again became acutely ill. She was hospitalized May 9, at midnight, with nausea, vomiting and abdominal pain, and the history of absence of bowel movements for the previous four days. The leukocyte count on admission was 6,500, with 12% neutrophils, 87% lymphocytes and 1% monocytes. The following morning the count was 11,750 leukocytes, with 78% neutrophils, 20% lymphocytes and 2% eosinophils. Intestinal obstruction was suspected, and laparotomy was done at 11:00 p.m. May 10; an adhesive band of omentum, causing a kink in the lower ileum, was released.

Blood transfusions, 300 c.c. each, were administered on the first and second postoperative days, 500 c.c. on the ninth postoperative day, and 300 c.c. on the twentieth postoperative day. Adrenal cortex solution (Eschortin) was given intravenously, beginning at 12:00 midnight on the second day after operation and continued until 6:00 p.m. of the third day. Four doses of 1 c.c. each were given every two hours initially, followed by three doses of 1 c.c. each every four hours (total, 7 c.c.). Frequent leukocyte counts varied from 18,450 on the third postoperative day to 6,300 on the eighth postoperative day; the neutrophil percentage fluctuated from 84 to 9 during this same time.

On the tenth postoperative day a purpura-like rash appeared over the face, arms and body generally. Radiologic reports mention enlargement of the heart on films made on the second, third, sixth and eleventh postoperative days, and enlargement of the liver on the sixteenth and eighteenth days after the operation. On the fourteenth day definite cardiac enlargement—11 cm. to the left of the midline—was noted clinically, with edema of the extremities. The patient's platelet count on the fourteenth day was 204,000.

Supportive therapeutic efforts, which included administration of sulfonamides, Prostigmine, digitalis and Coramine, were of no avail; the patient died on the twentieth postoperative day.

The final diagnosis recorded on the hospital chart included acute intestinal obstruction of the lower ileum due to adhesions, multiple perforations of the ileum, acute suppurative generalized peritonitis, pneumonia, and neutropenia of an undetermined type or cause. Unfortunately, diligent efforts to trace the autopsy report, said to confirm the stated final diagnosis, have been unsuccessful.

Case 2. A boy born in November, 1938, was first noted to have neutropenia in the summer of 1941, when he was about two and a half years of age. A blood count had been done at that time because his sister (case 1) had been found to have an abnormal blood picture. The boy had no symptoms referable to the neutropenia and had seemingly always been in good health. In April, 1942, his leukocyte count was 6,680, with 18% neutrophils, of which 7% were metamyelocytes, 74% lymphocytes, 7% monocytes and 1% basophils. Repeated examinations revealed persistence of this blood picture.

In 1943 the patient became critically ill, with fever and stomatitis; his temperature fluctuated between 99° F. and 105° F. during a period of six weeks. Physical observations were essentially normal except for an acute bilateral myringitis and an acute ulcerative stomatitis. The blood picture was characterized by neutropenia, relative lymphocytosis, and monocytosis; the erythrocyte count and hemoglobin value were slightly below normal. The test for heterophil antibodies was negative. The urine on several occasions contained a few erythrocytes and leukocytes. Patchy parenchymal infiltration was noted in a roentgenogram of the chest. Therapy consisted of the administration of penicillin, sulfadiazine, supportive intravenous fluids, and transfusions of blood. The patient had a stormy hospital course and did not fully recover until approximately three months after the onset of this illness. He

remained well for the ensuing six years except for mild infections of the upper respiratory tract at rare intervals. In 1949, at the age of 11, he received thyroid extract and methyltestosterone for obesity, hypogonadism, and hypometabolism. His development and physique became normal within the following year.

In March, 1951, when the patient was a little more than 13 years of age, he had pharyngitis, fever and lymphadenopathy. His leukocyte count at that time was 5,300, with 17% neutrophils, of which 3% were metamyelocytes, 61% lymphocytes, 20% monocytes, 1% eosinophils and 1% basophils. The pharyngitis lasted for a week, after which he recovered and was without symptoms. Repeated blood counts were done in June and July of that same year (table 1).

TABLE 1

Blood Counts in Patient with Chronic Neutropenia During 16 Years of Observation (Case 2)

Date	Leukocytes	% Neutrophils (% Metamyelocytes)	% Lymphocytes*	% Monocytes	% Basophils	% Eosinophils	Status
1942 Jan.	5,400	9 (1)	81	9	0	0	Asymptomatic
1942 April	6,680	18 (7)	74	7	1	0	Asymptomatic
1945 March	8,200	22 (0)	57	21	0	0	Ill
1948 Aug.	—	19 (1)	68	12	0	1	Asymptomatic
1951 March	5,300	17 (3)	61	20	11	1	Ill
1951 July	4,200	9 (0)	71	14	4	2	Asymptomatic
1955 Dec. 20	7,450	54 (12)	34	6	2	4	Ill
1955 Dec. 23	3,900	32 (1)	56	12	0	0	Ill
1956 Jan. 4	8,800	24 (0)	76	0	0	0	Ill
1956 Jan. 5, 12:50 a.m.	ACTH, 50 mg. administered intramuscularly						Ill
1956 Jan. 5, 8:50 a.m.	11,400	37 (3)	31	30	0	2	Improving
1956 Jan. 5, p.m.	Cortisone therapy started, 50 mg. every 6 hours orally						Improving
1956 Jan. 6	11,300	50 (0)	25	25	0	0	Asymptomatic
1956 Feb. 7	5,050	33 (0)	54	13	0	0	Asymptomatic
1956 July 7	4,750	31 (0)	57	10	0	2	Asymptomatic
1956 Dec. 20	5,500	40 (0)	59	1	0	0	Ill
1957 April 15	3,400	10 (1)	82	6	0	2	Asymptomatic
1958 April 4	4,800	19 (0)	60	18	0	3	Asymptomatic
1958 Sept. 9	5,250	31 (3)	57	9	1	2	Asymptomatic

* A review of these blood smears revealed that approximately half of the cells originally designated as lymphocytes were "monocytoid lymphocytes."

On December 16, 1955, the patient complained of headache, dizziness and fever. Physical observations were normal with the exception of a slight pharyngitis. He was treated for his symptoms but became worse the next day, so he was given penicillin intramuscularly, 400,000 units daily, for several days. On the fourth day a nonproductive cough developed, and râles were heard over the middle left lung field posteriorly. There was slightly cloudy infiltration in this same area in a roentgenogram of the chest. His blood count was 7,450 leukocytes, with 54% neutrophils, of which 12% were metamyelocytes, 34% lymphocytes, 6% monocytes, 2% basophils and 4% eosinophils. Tetracycline and nystatin (Mysteclin), 250 mg. every six hours, were started, the penicillin being continued. The patient's condition remained unchanged until the sixth day after onset of this illness, and then a tender, swollen red nodule about 3 cm. by 4 cm. appeared on the anterior surface of the left tibia, at the site of a bruise suffered two weeks previously during a football game. His temperature was 100° F., although the râles in the chest were clearing. The next day the nodule was larger, and the patient was hospitalized.

On admission to the hospital on December 23, 1955, his temperature was 101° F.; pulse, 100; respiration, 24 per minute; blood pressure, 110/72 mm. of Hg. The tender red swelling over the left tibia had increased in size (to 4 cm. by 5 cm.). Other physical observations were essentially normal. At times the cervical nodes and inguinal nodes were slightly enlarged and tender. The spleen was never palpable. During the next two weeks the temperature varied between 100 and 104° F.

The swelling on the left leg became larger, and on the second hospital day became fluctuant. Needle aspiration yielded 2 c.c. of serosanguineous fluid which, on culture, yielded alpha hemolytic streptococci and gram-negative diplococci. Small hemorrhagic blisters then appeared on the surface of the swelling; they became larger and confluent, forming a large bulla the edges of which gradually extended and became necrotic. On the eighth hospital day the blister was excised; it measured 8.5 cm. in greatest diameter. The pathologic diagnosis was intra-epidermal vesicle or bulla filled with white blood cells, keratinaceous debris and fibrin; no inclusion bodies or other diagnostic features were noted histologically. Normal healing did not take place, and a shallow indolent ulcer, measuring about 6 by 10 cm., without marginal induration or redness, remained at the site of excision.

Blood studies at the time of admission were recorded as follows: erythrocytes, 4,560,000, with 13.5 gm. hemoglobin; leukocytes, 3,900, with 31% neutrophils, of which 1% were metamyelocytes, 57% lymphocytes and 12% monocytes. Repeated blood counts revealed neutropenia, lymphocytosis and monocytosis (table 1). Platelets were adequate. Thorough laboratory study was carried out during this hospital stay, with the following observations:

The sedimentation rate (Westergren) was 42 mm. in one hour. Tests for the presence of L.E. cells were negative. Gram stain of material from the throat taken on the day of admission revealed rare gram-negative diplococci, and culture produced many *Neisseria catarrhalis,* alpha streptococci, hemolytic *Staphylococcus aureus,* a few nonhemolytic streptococci, and pneumococci; coagulase test of the staphylococcus was negative.

Normal values and/or reactions were obtained on urinalyses, blood cultures, tests for C-reactive protein, antistreptolysin "O" titer, agglutinations for typhoid O and H, paratyphoid A and B, Proteus OX19, and *Brucella abortus,* heterophil antibody agglutination test, serologic tests for syphilis, and cutaneous tests with coccidioidin and histoplasmin.

Blood chemistry studies were recorded as follow: Blood uric acid, urea nitrogen and plasma chlorides were normal. Total serum protein was 5.3 gm.; serum globulin, 2.0 gm. per 100 c.c.; the albumin-globulin ratio was 1.2 : 1.0. Paper electrophoretic analysis of the serum revealed albumin and the albumin-globulin ratio to be below normal, the alpha 1 globulin to be slightly elevated, and the presence of an abnormal alpha 3 component. The cephalin-cholesterol flocculation was 3 plus. The direct antihuman globulin test of Coombs was negative.

An electrocardiogram and roentgenograms of the chest and of the left leg were normal.

Antibiotic therapy was administered during the first nine days of hospitalization. At first penicillin, streptomycin and erythromycin were used, without evident benefit; tetracycline and nystatin (Mysteclin) were substituted, but discontinued on the ninth day because of the patient's severe diarrhea and perianal inflammation. The fever continued and stomatitis developed; a triple sulfonamide (Combisul) was therefore started.

On review of the peripheral blood smears during the first eight days of hospitalization the pathologist reported: "At the time of entrance, the picture was one of leukopenia with suppression of neutrophils; the lymphocytes ranged from normal-appearing to many monocytoid forms, the latter recently being fragile and difficult

to identify with certainty; no blast forms have been noted. The leukocyte count now is 10,000 with 78% lymphocytes, of which almost half are of the monocytoid type; 20% neutrophils of which 16% are metamyelocytes; 2% monocytes. The platelets are adequate and the erythrocytes are not remarkable. The picture most closely resembles infectious mononucleosis or hepatitis; moreover further observation is desirable to definitely rule out a leukemic disease."

On the ninth hospital day several hematologists were consulted, and varying opinions as to diagnosis were recorded, e.g., (1) infection secondary to recurrent

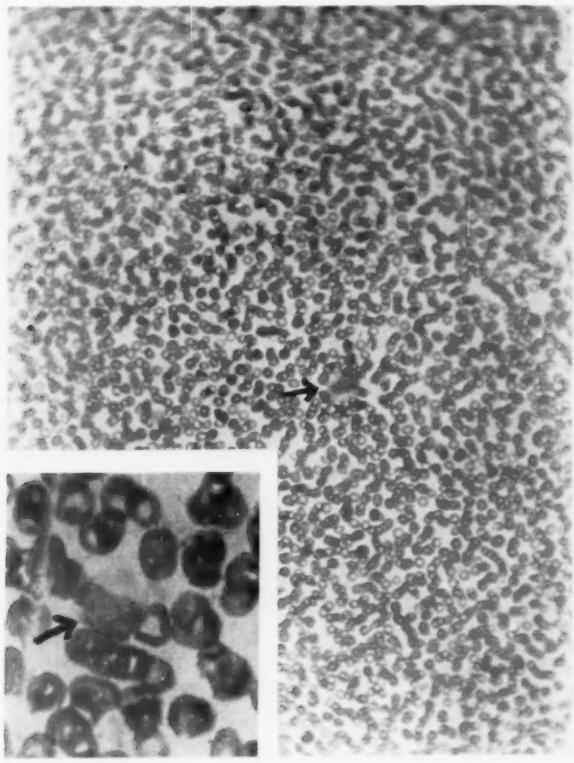

FIG. 1. Peripheral blood smear, December 29, 1955. Neutropenia. Inset shows monocytoid lymphocyte.

neutropenia; (2) the possibility of leukemia in view of the differential leukocyte count—23% monocytes, 52% lymphocytes, 24% neutrophils; (3) no specific diagnosis fits this picture now—preleukemic leukemia with possible spontaneous remission 10 years ago a good possibility; (4) the reported cases of cyclic neutropenia do not have lymphocytosis and monocytosis with exacerbations, as noted in this case.

On January 4, the thirteenth hospital day, bone marrow aspirated from the sternum was examined. First drop smears, buffy coat smears and touch preparations were made and stained with Wright's stain; spicules were fixed and stained with hematoxylin-eosin. The erythroid line and myeloid line were both represented

in normal maturation series, but both were quantitatively depressed. There were relatively profuse numbers of megakaryocytes fractionating into platelets which were normally granular; there were likewise numerous developing megakaryoblasts. The peripheral blood smear was one of very mild anemia, with sparse normoblastosis, granulocytopenia and monocytoid lymphocytosis. The pathologist's opinion was that there was no evidence of leukemia, lymphoma or granuloma, or evidence of specific organismal etiology in the bone marrow examined.

The leukocyte count the same day was 8,800, with 24% neutrophils and 76% lymphocytes, of which a considerable number were of the monocytoid variety.

On the fifteenth hospital day (January 5), at 12:50 a.m., when the patient's temperature was 104° F., he was given 50 mg. of ACTH intramuscularly. By morn-

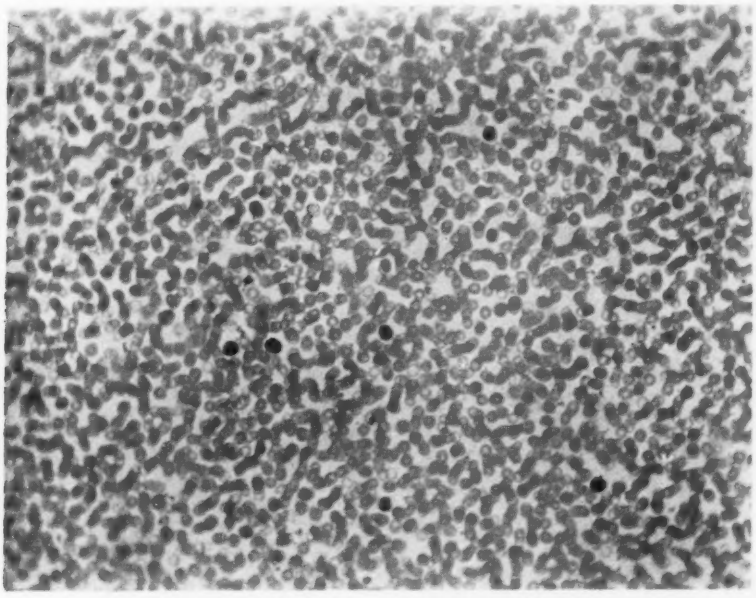

FIG. 2. Peripheral blood smear, January 7, 1956, after treatment. Demonstrates reappearance of neutrophils.

ing the leukocyte count had increased to 11,400, with 37% neutrophils, of which 3% were metamyelocytes, 61% lymphocytes, of which about half were of the monocytoid variety, and 2% eosinophils. That evening his temperature had dropped to 101° F., and he was placed on cortisone, 50 mg. every six hours orally. By the morning of January 6 (approximately 36 hours after initiation of the steroid therapy), his temperature had become normal, following a profuse diaphoresis. The leukocyte count was 11,300, with 50% neutrophils and 50% lymphocytes, of which half, again, were of the monocytoid variety. For the next few days the leukocyte count fluctuated between 5,000 and 6,000, with heavily granulated neutrophils and less fragility to the lymphocytes (figures 1 and 2). The fever abated and the cutaneous ulcer on the left tibia ceased to spread.

The cortisone was gradually reduced, on the seventeenth hospital day to 160 mg. daily, on the eighteenth to 140 mg., and on the nineteenth to 120 mg. At this time

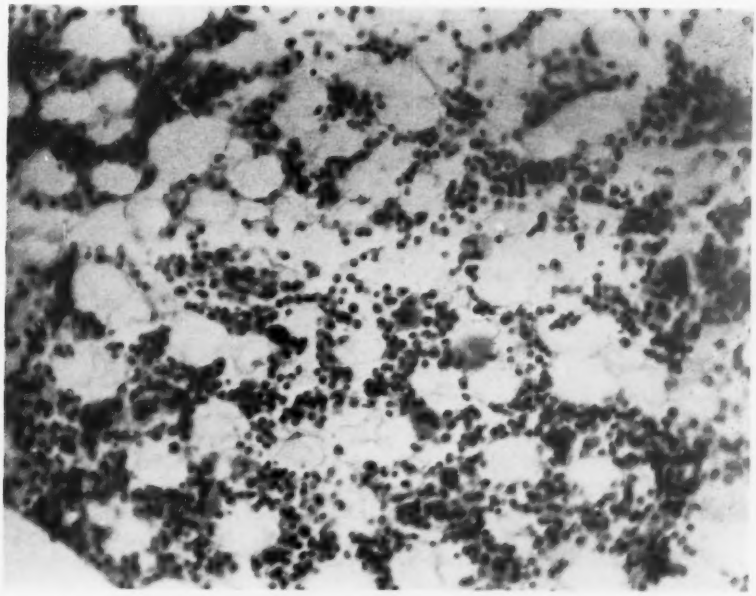

FIG. 3. Bone marrow, January 4, 1956. Hypocellular structure evident before treatment.

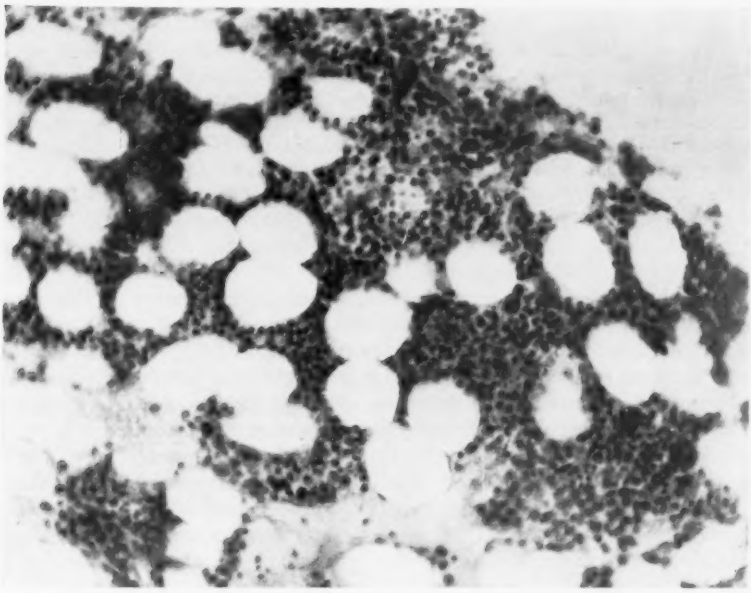

FIG. 4. Bone marrow, April 16, 1957. Normocellular pattern after recovery.

the patient's fever returned, the temperature rising to 101.2° F.; the cortisone was therefore increased to 160 mg. per day, whereupon the fever receded. The patient was discharged to his home on cortisone therapy on January 10, the twenty-first day of hospitalization.

Convalescence at home was uneventful. During a period of five weeks the cortisone was gradually reduced from 160 mg. per day to 2.5 mg. daily. The patient was given potassium and kept on an antipeptic ulcer régime. The cutaneous ulcer of the left tibia was treated locally with a 2% solution of gentian violet; a dry crust formed over the lesion, gradually healing and peeling off to leave a permanent scar. The patient had rapidly become moon-faced in appearance, but this subsided with decrease in steroid dosage.

On February 7, 1956, the leukocyte count was 5,050, with 33% neutrophils, 54% lymphocytes and 13% monocytes. The cortisone was discontinued on May 7, 1956.

The patient returned to school and did well until December 19, 1956, at which time he again suffered pharyngitis, with fever and chills. The leukocyte count was 5,500, with 40% neutrophils, 59% lymphocytes and 1% monocytes. He was given prednisone, 40 mg. one day and 20 mg. the next, and also tetracycline and nystatin (Mysteclin), 250 mg. four times daily for the same two days. Recovery was prompt and the patient has been well since then.

Follow-up studies have been recorded as follows: In February, 1957, absence of leuko-agglutinins in the serum was recorded; in March the urinary 17-ketosteroids were 5.8 mg. in 24 hours (normal, 9 to 22 mg.), and the urinary 11-oxysteroids were 13.3 mg. (normal, 8 to 25 mg.); paper electrophoretic analysis of the serum revealed the blood proteins to be normal.

In April, 1957, the leukocyte count was 3,400, with 9% neutrophils, of which 1% were metamyelocytes, 83% lymphocytes, 6% monocytes and 2% eosinophils. An eosinophil count of 25 dropped to zero four hours after intramuscular administration of 25 mg. of ACTH. Examination of bone marrow aspirate at this time revealed the erythroid, myeloid and megakaryocytic lines to be represented in normal maturation series and quantitatively normal (figures 3 and 4). There was a slight increase in hemosiderin-containing phagocytes. Buffy coat preparations of bone marrow contained numerous neutrophilic line cells, in contrast to buffy coat preparations of peripheral blood which were neutropenic. The patient was asymptomatic.

The patient has remained well since that time. A blood count April 4, 1958, recorded a leukocyte count of 4,800, with 19% neutrophils, 60% lymphocytes, 18% monocytes and 3% eosinophils.

Literature

A number of articles on neutropenia contain observations pertinent to a consideration of the disease in this sister and brother.

Chaiken[1] reported that in cyclic neutropenia, ACTH had no effect in raising the total leukocyte or neutrophil counts, and the neutropenic cycles could not be prevented by ACTH. However, when ACTH was administered, fever and stomatitis did not occur during the periods of neutropenia. Monto and his co-workers[2] described a 78 year old man with recurrent granulopenia in whom definite improvement clinically and in the blood and bone marrow occurred after administration of ACTH. Following splenectomy, symptomatic improvement occurred in this patient for the ensuing year of observation, although the neutropenic cycles recurred.

McMillin[3] reported a case of agranulocytosis attributed to a toxic depression of the bone marrow due to sulfadiazine therapy for cystitis and pneumonia. Dur-

ing the critical period in this patient's course the leukocyte count was 450, with complete absence of neutrophils; examination of the bone marrow revealed almost complete arrest of maturation of myeloid cells at the progranulocyte stage. After 48 hours of ACTH therapy the marrow had a few neutrophils; 10 days after cessation of ACTH therapy, biopsy of the bone marrow had no sign of maturation defect.

Spaet and Dameshek [4] reported four patients each of whom had had a chronic course of repeated infections, delayed healing of wounds, resistance to therapy, and paucity of symptoms during remissions. The skin and oral mucous membranes were involved in most of the infections. The patients had slight to moderate splenomegaly and a chronic, unvarying degree of neutropenia. Absolute lymphocytosis and monocytosis were usually noted. In each the bone marrow was essentially normal except for severe hypoplasia of the granulocytic precursors. Splenectomy, when performed, did not alter the course of the disease.

Bousser and Neydé [5] described a familial form of chronic neutropenia. These patients had an increased susceptibility to infection, and hypoplasia of the granulocytic elements of the marrow, but no splenic enlargement. The injection of 1 mg. of adrenalin caused a transitory increase to normal in the leukocyte count. None had any predisposition to serious infections.

Gänsslen [6] observed four families with neutropenia. The disorder was transmitted as a dominant inherited factor. It was not sex-linked, was noncyclic, and the patients did not have any serious infections.

Béguez César [7] collected a series of cases of chronic familial granulocytopenia transmitted as a recessive mendelian trait and characterized by albinism, irregular attacks of fever, nystagmus, leukopenia, granulocytopenia, lymphocytosis, and atypical protoplasmic inclusions in the leukocytes.

Discussion

In the differential diagnosis in both cases here reported, periodic or cyclic neutropenia [8] was strongly considered. This is a chronic disorder of the blood, characterized by the regular recurrence of neutrophilic granulocytopenia at approximately three-week intervals, with secondary constitutional symptoms, such as anorexia, malaise and fever, with stomatitis, pharyngitis, folliculitis, lymphadenitis and pneumonitis. Most of these factors were present in both of our patients, except that the neutropenia was a constant finding. No cyclic pattern was noted during the 14 months' observation in case 1, nor has a cyclic pattern to the neutropenia existed in case 2 during observation from the age of two and a half years until the present age of 19 years.

Aplastic anemia, thrombocytopenia and aleukemic leukemia were ruled out by the presence of normal erythropoiesis in the bone marrow and of platelets in normal amounts, and by the absence of bleeding diathesis in case 2. Furthermore, leukemic leukocytes were never found in the bone marrow or the peripheral blood smears. Hypersplenism was ruled out by the absence of hyperplasia of the bone marrow.[9]

Leukopenia associated with disseminated lupus erythematosus was considered in case 2 in view of the presence of this disease in the mother of these patients. However, L. E. cells were absent in the bone marrow and blood smears, and

other manifestations of lupus were not observed. The L. E. phenomenon was unknown in 1941, at the time of the first patient's illness.

A consideration of the etiology of the disease in the cases reported must include a possible relationship to the collagen diseases, not only because of the mother's history of lupus, but also because of the dramatic response in case 2 to treatment with the steroids. Although this may actually have been a spontaneous remission, the sudden cessation of fever, arrest in the necrotizing cutaneous lesion of the leg, and the dramatic change in the blood picture immediately following administration of ACTH and cortisone suggest that these benefits may be attributable to the steroid therapy. The influence of such a factor in case 1 is questionable. There was slight temporary improvement in the neutropenia in the latter case during a short trial of adrenal cortex solution, but this could have been due to the concomitant effects of blood transfusions, peritonitis, and the postoperative status of the patient. The splenectomy in case 1 apparently was of no benefit.

The therapeutic efficacy of ACTH and cortisone is well established in allergic hypersensitive states as well as in agranulocytosis. The recurrence of fever in case 2 on decreasing the dosage of cortisone too rapidly is further suggestive of its beneficial effect in adequate dosage. The urinary 17-ketosteroids three months after discontinuance of the steroid therapy were below normal.

The positive cephalin cholesterol flocculation test and abnormal blood proteins in case 2 were considered to be the results of cloudy swelling of the liver incident to the severe and prolonged fever. Normal results were obtained later when these tests were repeated while the patient was apparently in good health.

The possibility has been suggested that leuko-agglutinins are the immunologic mechanism responsible for the pathogenesis of certain types of neutropenia.[10, 11] Leuko-agglutinins, however, were not demonstrated in case 2 in February, 1957, when the patient was asymptomatic but neutropenic.

The "atypical" lymphocytes found in the peripheral blood smears in case 2 were of the "monocytoid" type, and resemble the Downey type I cell [12] found in infectious mononucleosis. These monocytoid lymphocytes are characteristic but not pathognomonic of infectious mononucleosis. They have been described in a variety of diseases, mainly of viral origin, including acute viral hepatitis, herpes zoster, roseola infantum, virus pneumonia, rubeola and rubella, as well as in undulant fever, rickettsial pox and allergic states. Litwins and Leibowitz [13] suggest that the presence of such cells in peripheral blood smears is a clue to the possible existence of virus infection. These abnormal lymphocytes have also been found in peripheral blood smears in experimental infectious hepatitis.[14]

Although the actual blood smears in case 1 are not now available for study, it is evident that some confusion existed in differentiating lymphocytes and monocytes. The differential counts of early blood smears, recorded in sequence, list variously lymphocytes or monocytes in excess of 50%. We presume that the "monocytoid lymphocytes" prominently noted in the leukopenic smears in case 2 undoubtedly were present also in case 1. They were noted in case 2 during febrile as well as during afebrile (asymptomatic) phases of the clinical course. Their significance is not known; however, a diagnosis of any of the aforementioned diseases in which monocytoid lymphocytes have been noted is not justified.

Summary

Two cases of chronic noncyclic neutropenia in siblings are presented. The first patient succumbed to sepsis in the presteroid era, whereas the second patient recovered rapidly from two febrile episodes with the use of steroid therapy. The urinary 17-ketosteroids were low in the second patient three months after discontinuing steroid therapy. The mother of these patients has disseminated lupus erythematosus, in remission with prednisone.

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Summario in Interlingua

Es presentate duo casos de chronic neutropenia non cyclic, non inducite per drogas, e non splenic. Le patientes esseva fraternos. Le matre de illes habeva disseminate lupus erythematose. Le curso clinic in ambe le pupos esseva characterisate per pauc variationes in le numeration hematocytic in despecto de recurrente attaccos de febre, gingivo-stomatitis, infectiones del vias respiratori, e ulcerationes del pelle superficial. Le diagnose differential imbracia neutropenia cyclic, depression toxic del medulla ossee per le effecto de drogas, anemia aplastic, thrombocytopenia, leucemia aleucemic, leucemia, hypersplenismo, disseminate lupus erythematose, mononucleosis infectiose, e leuco-agglutinemia.

Splenectomia e le uso de antibioticos e transfusiones de sanguine in le prime patiente esseva de pauc beneficio. Finalmente le patiente succumbeva a un sepsis irresistibile. Isto esseva ante le advento del steroides. Nulle splenectomia esseva effectuate in le secunde patiente, sed in despecto del therapia antibiotic e de altere mesuras supportative, nulle melioration occurreva in le condition clinic e hematologic del patiente usque ACTH e cortisona poteva esser administrate. Le patiente remaneva ben post le discontinuation gradual del therapia steroide in despecto del persistente neutropenia. Subsequentemente recurrente episodios de febrilitate respondeva promptemente al reintroduction temporari del therapia a steroides. Le valores del 17-cetosteroides urinari esseva infra le norma in iste patiente tres menses post le discontinuation del medication steroide.

Le possibilitate de un relation inter iste typo de neutropenia e le morbos de collageno es discutite. Es notate le presentia de lymphocytos monocytoide in frottis de sanguine peripheric. Le signification de illos non es cognoscite. Viste le excellente responsa obtenite per le uso de un therapia a steroides in le secunde del casos hic reportate, le mesme procedimento es recommendate pro simile casos de leucopenia.

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FATAL MILIARY COCCIDIOIDOMYCOSIS COMPLICATING PROLONGED PREDNISONE THERAPY IN A PATIENT WITH MYELOFIBROSIS *

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EXPERIENCE with ACTH, hydrocortisone and similar compounds during the last decade has repeatedly shown the risk of using these agents in large doses over long periods.[1, 2] This has been particularly true in tuberculosis and histoplasmosis, and in infections when its use is not accompanied with antimicrobial therapy.[3, 4] The following case is believed to be the first to document the deleterious effects of adrenocortical steroid therapy on clinical coccidioidomycosis.

CASE REPORT

In the third trimester of her first pregnancy, in 1950, this 37 year old white female was hospitalized for preeclampsia and found to have hepatosplenomegaly, anemia, neutrophilia with immature forms, nucleated red cells, and a hypocellular sternal marrow. It was presumed that she had agnogenic myeloid metaplasia. Following the delivery of a stillbirth a few weeks later, the patient was asymptomatic and in relatively good health. In April, 1955, she was examined during her second pregnancy and found to have the same physical and laboratory findings. She experienced no complications, however, and gave birth to a healthy male infant. Her case was

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reëvaluated in October, 1955, and despite an iliac crest biopsy, which showed myelosclerosis and fibrosis, Myleran (1,4-dimethanesulfonoxybutane, Burroughs Wellcome & Co.) therapy (6 mg./day initially, and 2 mg./day maintenance) was instituted for the revised diagnosis of chronic myelogenous leukemia. Three months later the white cell count had fallen from 40,000 per cubic millimeter to normal, and the drug was discontinued. In October, 1956, Myleran therapy was resumed because of recurrent leukocytosis. Two months later, however, it was discontinued because of thrombocytopenia. Physical examination at that time revealed pallor, hepatosplenomegaly, petechiae and ecchymoses. A tourniquet test was strongly positive. The white cell count was 9,500 per cubic millimeter, with immature forms; hemoglobin, 9.6 gm.%; hematocrit, 26%; circulating platelets, 6,000 per cubic millimeter. Sternal bone marrow aspiration was attempted, without success. Prednisone, 40 mg./day, was started because of the thrombocytopenic purpura.

Shortly thereafter the patient was admitted to Letterman Army Hospital, San Francisco, California, for the first time. Her general health appeared to be good, but there were obvious pallor and numerous petechiae and ecchymoses. The liver was palpable 5 cm. below the right costal margin in the midclavicular line. The spleen occupied the entire left upper quadrant and extended into the left lower quadrant 5 cm. below the level of the umbilicus. The tourniquet test was positive. Laboratory studies disclosed a pancytopenia: white cell count, 3,800 per cubic millimeter, with juveniles and 16% monocytes and 5 nucleated red cells/100 white cells; hematocrit, 28%; circulating platelets, 21,000 per cubic millimeter. Other studies revealed a negative serologic test for syphilis and a negative Coombs' test; normal urinalysis, chest x-ray, fecal urobilinogen, bleeding time, coagulation time, prothrombin time, and osmotic fragility test; virtually absent clot retraction, and x-ray evidence of myelosclerosis. An iliac crest aspirate was hypocellular. All available blood and marrow preparations were reviewed, and it was felt that the condition was actually leuko-erythroblastosis due to myelosclerosis and myelofibrosis. In an attempt to combat the clinical manifestations of the pancytopenia, prednisone (40 mg./day) was continued.

There was no change in the degree of leukopenia or thrombocytopenia, but the anemia became progressively more severe and required increasingly frequent blood transfusions to maintain the hematocrit above 20%. No evidence of bleeding could be found after the purpura was controlled, and it was assumed that the progressive anemia was due to a superimposed hemolytic process. Accordingly, consideration was given to splenectomy, and radioiron studies were done to evaluate the role of the spleen in hematopoiesis versus red cell destruction. The following results were obtained: (1) erythrocyte life span was 16 days; (2) erythropoiesis increased approximately threefold; (3) bone marrow erythropoiesis comprised approximately one third of the total; (4) splenic erythropoiesis accounted for the remaining two thirds of the total, but there were marked splenic sequestration and destruction of erythrocytes. In view of these findings, it was believed that the hematopoietic function of the spleen outweighed its destructive effect, and that splenectomy was not indicated.

In February, 1957, the patient noted increasing weakness, intermittent nausea, myalgia and arthralgia. There were intermittent episodes of low grade fever (99 to 100° F.) which gradually became more frequent, reaching 103 to 104° F. daily by June, 1957. Repeated physical examinations, chest x-rays, and cultures of the nose, throat, urine and blood prior to and during her last admission, in June, 1957, failed to reveal the origin of the fever. Hematologic studies were unchanged. The patient was maintained on 10 mg. of prednisone four times daily, and remained ambulatory. She did not appear to be acutely ill or toxic, in spite of temperature elevations to 104° F. daily. A chest x-ray on June 21, 1957, was normal, but fine miliary densities were noted throughout all areas of both lung fields in the chest roentgenogram

of July 8, 1957. At this time her daily temperature elevations were reaching 105 to 106° F., and streptomycin, para-aminosalicylic acid, isonicotinic acid hydrazide and pyridoxine therapy was started. The first and second strength purified protein tuberculin tests were negative at this time, as were the histoplasmin and coccidioidin skin tests. Examinations of the urine and spinal fluid were normal, and smears for acid-fast bacilli were negative. The patient was not raising sputum for diagnostic purposes, so several gastric aspirations were obtained for study. After 10 days, viomycin was added to the antituberculous program, due to lack of temperature response and evidence of progression in serial chest films. The patient did not appear to be critically ill until 48 hours prior to death, when she developed severe dyspnea, cyanosis, tachycardia and terminal hypotension. Her death occurred exactly seven years after the initial diagnosis of myelofibrosis.

Postmortem Findings: At autopsy, numerous petechial hemorrhages were present over the entire body surface, buccal mucosa, conjunctivae and gastric mucosa. "Moon" facies and a prominent dorsal fat pad were observed. There was a minimal degree of generalized lymphadenopathy. Innumerable small, firm yellow nodules, measuring 5 to 10 mm. in diameter, were observed in the lungs, mediastinal nodes, liver, spleen, omentum and kidneys. The lungs appeared to be diffusely hemorrhagic on cut section. Massive hepatosplenomegaly and marked adrenal atrophy were the other significant findings on gross examination.

Smears and cultures of both lungs were negative for acid-fast organisms. Lung cultures grew *Coccidioides immitis.*

Microscopic sections of all lobes of the lungs showed alveoli filled with edema fluid, erythrocytes, mononuclear cells, lymphocytes, plasma cells and polymorphonuclears. Fibrin accumulations within the alveoli were closely applied to the septa forming hyalin membranes. The septa were thickened, congested and infiltrated by chronic inflammatory cells and a few granulocytes. Foci of necrosis were prominent. In many areas there were early epithelioid tubercles with Langhans' giant cells containing spherules of *C. immitis.* Similar miliary-type Coccidioides tubercles were found in the liver, spleen, omentum, kidneys, bone marrow and meninges. Extramedullary hematopoiesis was prominent in the lungs, liver, spleen, lymph nodes and renal capsules. Hemosiderin was present in large quantities throughout the entire reticuloendothelial system. The adrenal cortices were atrophic, while the pituitary was not altered. Sections of rib, sternum, vertebrae, calvarium and ilium revealed diffuse myelosclerosis and myelofibrosis.

Discussion

Adrenocortical steroid therapy was initiated in this patient eight months prior to death because of myelosclerosis and myelofibrosis with thrombocytopenia and a complicating acute hemolytic anemia. Recurrent febrile reactions of unknown origin began two months later. Four and one-half months elapsed from the onset of fever until faint miliary densities appeared on chest x-rays. The patient remained ambulatory and did not appear to be toxic or acutely ill until 48 hours prior to death. It was suspected that prednisone was modifying the clinical picture and delaying objective evidence of the source of fever for many weeks or months. This posed a diagnostic and therapeutic dilemma. It was assumed that prednisone had suppressed the patient's own adrenal function, and withdrawing this therapy in the face of a severe but undiagnosed febrile illness might have been disastrous. Accordingly, she remained on prednisone until her death.

The patient was thought to have miliary tuberculosis during her terminal illness and even at the time of the autopsy. It was not until microscopic and bacteriologic studies were completed that the correct diagnosis of disseminated coccidioidomycosis was made. As might have been anticipated, the coccidioidin skin test was negative in the presence of high fever, prednisone therapy, and miliary pulmonary disease.

A residential history was obtained from the patient's husband and, as far as could be ascertained, she had never lived in or visited the usual endemic areas of coccidioidomycosis, although she had lived on the fringe of these areas for several years. It is of interest that coccidioidin skin tests performed both on her husband and on her 20 month old son were negative. It must be presumed that weeks or months prior to dissemination the patient had become infected, perhaps from agricultural or other products from an endemic area.[5] It is also possible that a dormant process had been present for many years and that it was activated by adrenocortical steroid therapy.

Experimentally, Cavallero and Sala [6] studied the effects of cortisone on coccidioidomycosis in rats. *C. immitis* was injected subcutaneously into control rats and into rats receiving cortisone. In contrast to the control animals, who manifested local granulomatous reaction without generalized infection, the cortisone-treated animals tended to show diffuse infection involving the spleen and lungs. On the other hand, Newcomer and his associates [7] concluded that cortisone had only a minimal adverse effect on coccidioidomycosis in rats, and they suggested that the dose of adrenal steroids employed might be a significant factor in the differences noted by various investigators.

Clinically, adrenocortical steroids have been used without success by Engleman and Krupp [8] in treating a fatal case of disseminated coccidioidomycosis. Levan and Einstein [9] reported on the therapeutic use of oral cortisone in 19 patients with erythema multiforme and/or erythema nodosum associated with primary coccidioidomycosis. A total dose of 350 to 775 mg. was administered over a four- to six-day period to a heterogeneous group whose ages ranged from 11 to 50 years, and among whom were one Negro and two patients of Mexican extraction. An excellent immediate response was noted in the allergic skin manifestations of coccidioidomycosis, and no patient manifested evidence of dissemination. The authors made a survey of medical opinion in Kern County, California, and did not learn of a single instance of dissemination of coccidioidomycosis while patients were receiving adrenocortical steroid therapy for some other reason. It was emphasized in this report, however, that the duration of steroid therapy was brief, the number of cases limited, and the possibility of deleterious effects could not be discounted on the basis of experience to date. Our case bears out the caution expressed by Levan and Einstein in their study.

Summary and Conclusions

The first reported case of disseminated coccidioidomycosis associated with adrenocortical steroid therapy is documented in a patient with a seven-year history of myelofibrosis. This report highlights the possible danger of acquisition, activation or dissemination of coccidioidomycosis when steroid therapy is pro-

longed, and is considered to be the counterpart of observations recorded with reference to tuberculosis, histoplasmosis and other infectious diseases.

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SUMMARIO IN INTERLINGUA

Le periculos del uso de ACTH, hydrocortisona, e simile compositos in grande doses durante longe periodos de tempore ha essite clarmente demonstrate in le curso del passate decennio, specialmente in le caso de infectiones sin concomitante therapia antimicrobial. Tamen, coccidioidomycosis disseminate associate con prolongate therapia a steroide adrenocortical ha non previemente essite reportate. Le presente articulo concerne un tal occurrentia in un femina de racia blanc de 37 annos de etate con un septenne historia de myelofibrosis. Therapia steroide esseva initiate in iste patiente octo menses ante su morte a causa del disveloppamento de thrombocytopenia e acute anemia hemolytic. Recurrente reactiones febril de origine incognoscite comenciava duo menses plus tarde, e densitates miliari appareva in roentgenographias thoracic tres septimanas ante su morte. Esseva supponite que illa habeva tuberculose miliari, e un vigorose therapia antituberculotic esseva administrate, sed sin responsa clinic. Le therapia steroide esseva etiam continuate a causa del supprimite function suprarenal in le patiente. Illa non pareva esser criticamente malade usque 48 horas ante su morte, quando illa disveloppava sever grados de dyspnea, cyanosis, tachycardia, e hypotension terminal. Mesmo al tempore del necropsia il esseva opinate que illa habeva tuberculose miliari. Il esseva solmente post le completion del studios microscopic e bacteriologic que le correcte diagnose de coccidioidomycosis disseminate poteva esser establite. Assi le presente reporto pone in relievo le risco del acquisition, activation, o dissemination de coccidioidomycosis in le uso prolongate de un therpia steroide e es considerate como un complemento del observationes reportate con respecto a tuberculose, histoplasmosis, e altere morbos infectiose.

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TYPHOID FEVER COMPLICATED BY INTESTINAL PERFORATION AND MYOCARDITIS *

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THE reported incidence of typhoid fever has diminished greatly in the last 20 years. With public health education, accurate methods of diagnosis and the presence of efficacious antimicrobial therapy, typhoid fever does not cause the dreaded mortality rate or disastrous complications of the past. Yet severe cases of typhoid fever are occasionally encountered.

The following case report is an example of an overwhelming infection due to *Salmonella typhosa* from which the patient recovered. The clinical course was complicated by intestinal perforation and acute pulmonary edema due to "typhoid myocarditis."

CASE REPORT

A critically ill 21 year old white male house painter was admitted to the University Hospital at 4:10 p.m. on March 23, 1957. A fragmentary history was obtained from relatives because the patient was disoriented. He was known to have visited in rural areas of Arkansas and Mississippi four weeks prior to admission. While on this trip he drank "spring water." There was no recognized exposure to typhoid fever or other febrile diseases. Approximately three weeks before admission he developed loose stools. The following day periumbilical abdominal discomfort was noted, associated with fever but no chills. Anorexia, malaise and weakness developed shortly thereafter. During the week before admission the abdominal pains became colicky and were generalized. The fever continued, with the development of chills, nausea and vomiting. For three days prior to admission the patient retained no food or fluid. The diarrhea became almost continuous, with watery, brownish movements every 20 to 30 minutes. No blood was seen in the stools. A slightly productive cough developed. No rash was noted.

Two days before admission the patient was seen by the referring physician, who noted marked dehydration and malnutrition, with severe generalized abdominal tenderness. Penicillin, streptomycin and paregoric were given, without improvement. He was then referred to the University Medical Center.

During childhood he had had measles, chickenpox and pertussis, but no rheumatic fever, diphtheria or serious illnesses. The extent of previous immunizations was not known.

Examination on admission revealed a blood pressure of 130/40 mm. of Hg; pulse, 80 and regular; temperature, 102° F. (oral); respiratory rate, 34. The patient was well developed but appeared to be poorly nourished, markedly dehydrated, and both acutely and chronically ill. Mental confusion and belligerent behavior necessitated the use of restraints. Many 2 to 3 mm. erythematous, slightly elevated spots which blanched under pressure were found on the trunk. There was no pharyngeal hyperemia. The neck revealed no venous distention. The lung fields were clear to percussion and auscultation. No cardiac enlargement was found, and the heart

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sounds were of good quality, with no murmurs heard. The abdomen was slightly protuberant and hyperresonant. Diffuse abdominal rigidity and tenderness were noted, without demonstrable rebound. There was no detectable hepatomegaly, splenomegaly or free peritoneal fluid. The bowel sounds were hypoactive. The genital and rectal examinations were normal. Aside from the obvious delirium, the neurologic examination was normal.

Admission laboratory studies revealed a urine pH of 5.0, specific gravity of 1.024, and a trace of albumin and glucose (5% dextrose solution was being given intravenously when the specimen was obtained). A few fine granular casts and numerous bacteria but no erythrocytes or leukocytes were seen on microscopic examination. The hemoglobin was 14 gm., with a hematocrit of 42 vol. %. The peripheral white blood cell count was 9,000, with 82% segmented cells, 10% band forms, 1% monocytes and 7% lymphocytes. The nonprotein nitrogen was 64 mg. %; serum glucose, 146 mg. %; chlorides 102 mEq.

An admission x-ray (figure 3A) of the chest revealed no cardiac enlargement. The lung fields were clear except for an artifact in the right apex. No subdiaphragmatic air was seen in the chest or erect abdominal films, though there was a suggestion of hepatic enlargement. No air fluid levels were seen.

A tentative diagnosis of typhoid fever was made. Therapy was begun after obtaining cultures of the blood, urine and feces. One gram of chloramphenicol was given intramuscularly every eight hours. In addition, dehydration was corrected during this time with 3 L. of 10% dextrose in water, with 80 mEq. of potassium chloride, 1 L. of 5% dextrose in Ringer's lactate, and 2 L. of 10% dextrose in physiologic saline. There was a gradual fall in temperature to 99° F. Morphine sulfate was administered to control diarrhea.

On the following day, 20 hours after admission, the abdominal pain became accentuated. Because of increasing abdominal distention and inaudible bowel sounds, emergency supine and erect x-rays were obtained. The presence of free air under each diaphragm, with no evidence of mechanical obstruction, confirmed the clinical diagnosis of a perforated viscus.

Bacteriologic data available at this time revealed a gram-negative bacillus in the blood cultures, and colonies of gram-negative bacilli in the stool cultures which did not ferment lactose. The urine cultures were sterile. Organisms from the stool culture were agglutinated by polyvalent and group D Salmonella antisera. A diagnosis of typhoid fever with intestinal perforation was thus substantiated bacteriologically.* Medical management was felt to be unwise, since a large perforation was suspected. The surgical service agreed to perform an emergency laparotomy.

Prior to surgery the patient's blood pressure had remained stable at 120/60 mm. of Hg, although the pulse rose to 100 (figure 1). There was no other change in his physical status. In view of his grave condition and the additional stress to be imposed by a major surgical procedure, it was elected to initiate therapy with adrenal steroids. He was begun on 100 mg. of hydrocortisone intravenously every eight hours and 50 mg. of cortisone acetate intramuscularly every six hours.

Approximately 28 hours after admission an exploratory laparotomy was performed under endotracheal anesthesia. Evidence of a generalized infection was encountered upon opening the peritoneal cavity, and a moderate amount of free fluid was found to be present. (Cultures subsequently revealed only *Escherichia coli.*) A perforation 2 cm. in diameter was found about 4 cm. proximal to the ileocecal valve. The omentum had not sealed off the perforation. The edges of the ulcer were friable and necrotic. Two other small areas of serosal necrosis involved the

* Subsequent biochemical studies confirmed the serologic identification. The organisms were identified by the Communicable Disease Center, Chamblee, Georgia, as *Salmonella typhi*, phage type C. Degraded VI.

terminal ileum. There were a number of enlarged lymph nodes and areas of necrosis in the omentum. The perforation was closed with an inverting Connel suture, reinforced with running catgut suture and the Halsted mattress suture. The omentum was pulled over the terminal ileum after the perforation was closed. Two large Penrose drains were placed in the lateral gutters. He withstood the procedure well.

Postoperatively the patient was continued on 100 mg. of hydrocortisone intravenously every eight hours, 1 gm. of chloramphenicol intravenously every six hours (after 24 hours this was changed to 1 gm. intramuscularly every six hours),

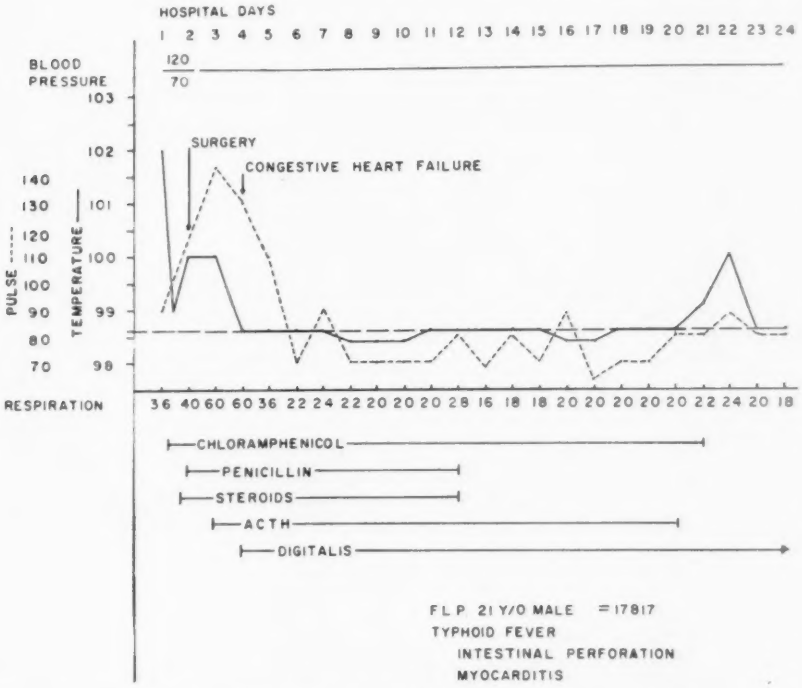

FIG. 1. A graphic record of the hospital course of the patient.

900,000 units procaine penicillin intramuscularly every 12 hours, 300,000 units of crystalline penicillin every three hours, and 0.5 gm. streptomycin every 12 hours. Continuous gastric suction was maintained.

During the first postoperative day the patient was still confused and had to be restrained. Forty units of intramuscular ACTH gel daily were begun in the hope of rapidly reducing the hydrocortisone. The temperature increased to 101° F. (rectal), with a pulse of 140 and respiration of 30 (figure 1). The blood pressure remained at 120/60 mm. of Hg, with a 24-hour urinary output of 1,100 c.c. Expiratory wheezes were heard in the left lateral chest, but no cardiac dysfunction was noted. The blood chlorides were 98 mEq.; carbon dioxide combining power, 23 mEq.; potassium, 4.6 mEq.; sodium, 125 mEq.; nonprotein nitrogen, 43 mg.%; hematocrit, 38 vol. %; hemoglobin, 14.5 gm. The patient was given 2 L. of dextrose

and water, and 1 L. of dextrose and isotonic saline, plus 40 mEq. of potassium, and multivitamins.

On the second postoperative day there was obvious deterioration. The respiratory rate had increased to 55 per minute, and there was extreme air hunger, with flaring of the alae nasi and use of all accessory respiratory muscles. The pulse persisted at 140 per minute, but it remained regular, and there was no change in blood pressure (figure 1). Fine moist râles were heard at the lung bases posteriorly. No cardiac enlargement was found. An apical diastolic gallop rhythm was present,

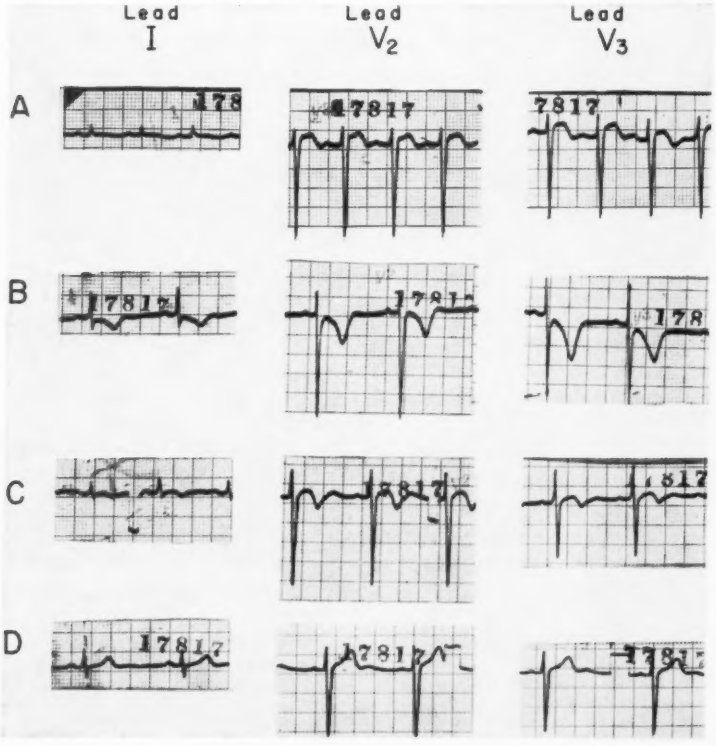

FIG. 2. A. March 26, 1957, the third day of hospitalization and the day of acute pulmonary edema. B. April 8, 1957, 16 days after the onset of pulmonary edema. C. May 8, 1957, 46 days after the onset of pulmonary edema. D. February 11, 1958, 10 months after hospitalization.

but no murmurs were detected. An electrocardiogram revealed a sinus mechanism with a ventricular rate of 112; PR interval, 0.16 second; QRS, 0.06 second; QT, 0.30 second. There was elevation of the ST segments in V_{1-4}, negative T in AVL with a flat T in Lead I (figure 2A). An x-ray of the chest revealed a normal cardiac silhouette, with densities radiating from each hilar area suggestive of acute pulmonary edema (figure 3B). It was obvious that myocardial failure had developed. Digitoxin was administered intramuscularly, 0.4 mg. every four hours, until a total of 1.2 mg. had been given. Mercaptomerin (Thiomerin), 1.0 ml., was given intra-

muscularly, and nasal oxygen was started. Twelve hours later the patient appeared to have improved, with respirations of 36 per minute and a pulse rate of 86 and regular; the gallop rhythm was no longer heard.

The following day (third postoperatively) disorientation persisted but the vital signs remained normal. Electrocardiographically the rate was 72, with a sinus mechanism. The T waves were negative in Leads II, V_{1-5}, and were interpreted

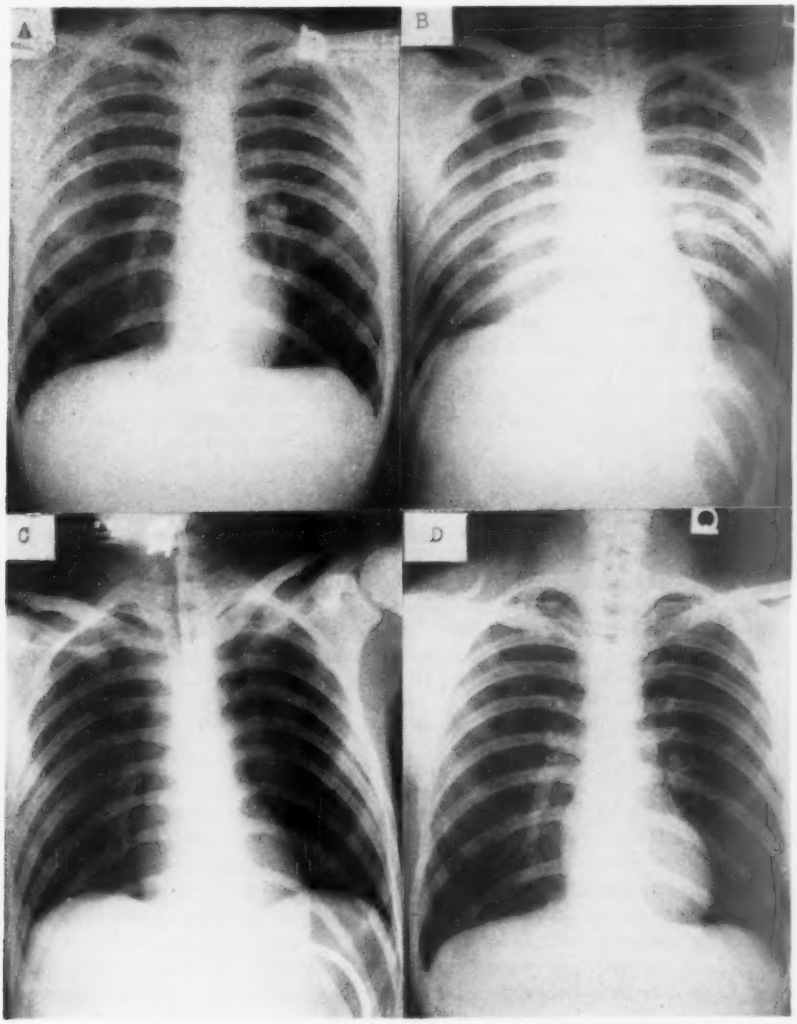

FIG. 3. A. March 23, 1957, day of admission to the hospital. B. March 26, 1957, the third day of hospitalization and the day of acute pulmonary edema. C. March 28, 1957, five days after admission and two days after the onset of pulmonary edema. D. February 11, 1958, 10 months after admission to the hospital.

as suggestive of anterior myocardial "ischemia." Fluid and electrolyte balances were maintained, and medications, including 0.1 mg. digitoxin daily, were continued. On the fourth postoperative day the patient was much clearer mentally. By the sixth day after surgery he was completely rational and did not require restraints. Normal spontaneous bowel movements had occurred. Gastric suction was discontinued, and he was permitted to take surgical liquids.

On the eighth postoperative day all surgical drains were removed. The patient continued to improve, with a gain in strength and appetite. The electrocardiogram continued to show sagging ST segments in Leads II, III, AVF and V_{2-5}, with inversion of the precordial T waves. Steroid therapy was gradually reduced and finally tapered off with decreasing doses of ACTH. By the eleventh postoperative day all antibiotics except oral chloramphenicol, 1.0 gm. daily, had been discontinued.

On the thirteenth and sixteenth postoperative days the stool cultures were negative for *S. typhosa*. Nineteen days after surgery an electrocardiogram showed depression of the ST segments, with T wave inversion as before (figure 2B). Chloramphenicol was stopped at this time (the twentieth day of therapy), but digitoxin was continued.

At the time of the patient's discharge, on April 14, 1957, 22 days after admission, although fully ambulatory he was instructed to continue digitalis and gradually to increase his physical activity. When seen as an out-patient three days after discharge he was free of symptoms, with no noticeable intolerance to exercise. A soft systolic murmur was heard at the apical area for the first time, but there was no evidence of a gallop rhythm. An electrocardiogram was unchanged (figure 2C). Stool cultures continued to be negative for *Salmonella typhosa*.

When the patient was next seen, six weeks after admission, he professed to be well, with no symptoms related to the cardiovascular system. The soft systolic murmur at the apex persisted, but physical examination was otherwise normal. Inversion of T waves in the chest leads persisted.

On February 11, 1958, approximately 10 months after discharge from the hospital, the patient was requested to return for follow-up examination. Over the last 10 months he had regained his normal "pre-illness" weight of 135 pounds, and was completely asymptomatic. The blood pressure was 128/66 mm. of Hg; pulse, regular and 64 per minute; respiration, 18 per minute; oral temperature, 98° F. There was no detectable cardiomegaly, but a soft systolic apical murmur was heard. No hepatosplenomegaly or lymphadenopathy was found.

The urine revealed a specific gravity of 1.015 and a 1 plus albuminuria, with a negative test for sugar. No cells were seen on microscopic examination. The electrocardiogram (figure 2D) and chest x-ray (figure 3D) were reported as normal.

Discussion

Untreated typhoid fever of three weeks' duration is rarely encountered in the United States. In such cases, a greater incidence of complications is to be expected than when chloramphenicol therapy has been instituted early.

The clinical manifestations of infections caused by *Salmonella typhosa* are due in part to endotoxin released from the somatic portion of the bacterium.[1] Endotoxin obtained from killed organisms has been shown to produce marked generalized vascular injury in experimental animals.[2] In humans, *Salmonella typhosa* endotoxin is believed to be responsible for the chills, fever, leukopenia, hypotension, delirium, hepatitis and myocarditis seen in typhoid fever.[3, 4]

Cardiovascular abnormalities other than hypotension have not been mentioned as a common complication of typhoid fever. When noted, the myocardial damage was thought to be a sequel to prolonged fever and inanition. A number

of years ago Thayer attributed the development of arteriosclerosis and its complications to preceding infections by the typhoid bacillus.[5] Toxic myocarditis was found in less than 2% of a large number of patients with typhoid fever.[6]

It is of interest that abnormal electrocardiograms were found in 40 to 50% of patients with typhoid fever before chloramphenicol therapy became available.[7, 8] No data are available relevant to this point since the advent of specific antimicrobial therapy. The most commonly reported abnormalities were changes of the T waves and prolongation of the PR interval. The abnormalities were detected between the ninth and the fortieth days of illness, but generally disappeared within three weeks after recovery.[7, 8, 9] Occasionally they lasted for as long as three months.

Clinically, myocardial involvement was manifested by tachycardia, pendular rhythm, diastolic gallop, hypotension, pulmonary congestion, hepatomegaly, edema and the abovementioned electrocardiographic changes.[9] (Hypotension does occur without evidence of myocardial injury, probably as a result of peripheral vasodilation produced by fever.) Unless there was preëxisting vascular disease, objective evidence of myocardial damage was transient and not recorded, since collateral channels probably maintained adequate coronary blood flow.[10]

Postmortem study of hearts from patients dying during typhoid fever revealed a generalized involvement of the coronary vascular tree. There was evidence of injury to the endothelium of arterioles and capillaries with occluding thrombi. Focal areas of degenerated myocardial muscle were found throughout the heart.[2, 10]

The recorded incidence of congestive heart failure during typhoid fever has been very low, and usually occurred following intestinal perforation in association with preëxisting heart disease, or as a terminal event. Cardiac failure usually developed suddenly and was resistant to the classic forms of therapy.[6, 9] There are no clinical data concerning the influence of adrenal steroids on this problem.

Cardiac decompensation as a result of myocardial injury by *Salmonella typhosa* endotoxin was exemplified by this patient. Acute cardiac failure occurring postoperatively in this patient developed despite prior treatment with chloramphenicol and hydrocortisone. Dehydration of an extreme degree led to vigorous efforts at correction; however, it was not felt that his needs were exceeded. Excessive hydration during the first two days of hospitalization apparently did not lead to cardiac failure. Sodium chloride was used sparingly, and the hematocrit did not decline precipitously. Electrolyte studies were not obtained prior to cardiac failure, but significant depletion must have existed, in view of the long history of diarrhea and vomiting. There was no evidence of electrolyte imbalance after measures to improve cardiac function had been inaugurated. Anoxia, which might have caused temporary myocardial ischemia, was not noted during surgery or during recovery from anesthesia. Finally, since there was no known preëxisting heart disease, it seems reasonable to conclude that cardiac failure in this case was probably due to myocardial damage from *Salmonella typhosa* endotoxin.

Early recognition of the cardiac failure may have been responsible for the prompt response to digitalis therapy. There was marked slowing of respiration, with clearing of the lung fields and prompt disappearance of the gallop rhythm.

It is an intriguing possibility that hydrocortisone may have enhanced the response to digitalis. Since digitalis is of steroid configuration, there is reason to suspect that adrenal steroids may influence myocardial integrity. The anti-inflammatory action of steroids, particularly in typhoid fever, is well documented and may have exerted a protective effect on the myocardium in this instance.[11, 12]

In subsequent examinations the heart size remained within normal limits and the sounds were of good quality. A grade I apical systolic murmur was detected for the first time during the follow-up period. Since exercise tolerance had not been limited, digitalis therapy was discontinued. It is of interest that the T wave changes had reverted to normal by the 10-month follow-up examination.

In recent years there has been a trend to conservative management of perforations of the small intestine as a result of typhoid infections, rather than to resort to surgical closure. The availability of broad-spectrum coverage has made such therapy possible. It is significant that there has been no notable change in mortality rates associated with this approach, although the number of patients so treated has been small. Small perforations probably occur in typhoid fever, with minimal leakage of intestinal contents into the peritoneal cavity. Such cases can and perhaps should be handled conservatively with broad antimicrobial coverage.

Surgical intervention in the case reported here may not have been mandatory, since cultures from the peritoneal cavity obtained at operation revealed a highly sensitive strain of *Escherichia coli*, with no growth of *Salmonella typhosa*. The detection of free air beneath the diaphragm, however, indicated a large perforation. Since the patient was desperately ill and a poor risk to cope with a generalized peritonitis, closure of the perforation was thought advisable. The necessity for surgery was perhaps further emphasized by the finding that the omentum had not sealed off the perforation.

As a final point, adrenal steroids have an established place as an adjunct to antimicrobial therapy in typhoid fever since they profoundly reduce the degree of intoxication. Hydrocortisone in this instance was thought to have been life-saving in view of the severity of our patient's illness.

Summary

A case of typhoid fever has been presented. The course of this patient was complicated by intestinal perforation and by toxic myocarditis with acute myocardial failure.

The disease and its complications responded dramatically to the therapy described.

Summario in Interlingua

Le reportate incidentia de febre typhoide ha grandemente diminute in le curso del passate 20 annos, e gratias al therapias antimicrobial in nostre dies, complicationes es inusual.

Le presente reporto concerne le caso de un masculo de racia blanc de 21 annos de etate qui esseva criticamente malade con un infection per *Salmonella typhosa*. Le curso clinic esseva complicate per un perforation del ileum terminal. Isto esseva claudite chirurgicamente. Ben que le majoritate del perforationes causate per infec-

tiones per *Sal. typhosa* pote esser tractate facile- e salvemente con efficace agentes antimicrobial a large spectros, le serie condition de iste patiente rendeva le clausion chirurgic urgentemente indicate. Quaranta-octo horas post le operation le patiente disveloppava acute edema pulmonar. Un electrocardiogramma revelava elevation del segmento ST con inversion de unda T, suggerente "ischemia" myocardial compatibile con un diagnose de myocarditis. Le patiente respondeva dramaticamente al tractamento con digitoxina, mercaptomerina, e oxygeno nasal, con continuation del steroides que habeva essite initiate ante le operation. Al examine 10 menses post le hospitalisation, nulle residue anormalitate esseva detegibile.

Myocarditis toxic ha essite observate in minus que 2% de un grande numero de patientes con febre typhoide. Nulle datos del toto es trovabile con respecto a iste puncto depost le advento de specific therapias antimicrobial. Usualmente, le damnos myocardial occurrente in febre typhoide e detegibile per medios electrocardiographic es de character transitori. Isto es probabilemente le consequentia de un rapide disveloppamento de canales coronari collateral. Microscopicamente, injuria del endothelio in arteriolas e capillares con thrombosis e areas focal de degenerate musculo myocardial ha essite reportate.

In le hic-presentate caso, il pare justificate supponer que le steroides suprarenal ha preservate le integritate myocardial per se, a parte su effecto protectori super le myocardio como resultato de su action anti-inflammatori.

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EDITORIALS

THE BULLETIN OF THE AMERICAN COLLEGE OF PHYSICIANS

Upon the recommendation of the Board of Editors of the ANNALS OF INTERNAL MEDICINE, the Regents of The American College of Physicians, in April, 1959, authorized a new publication, to be called THE BULLETIN OF THE AMERICAN COLLEGE OF PHYSICIANS.

The BULLETIN will contain the material which up to the end of 1959 was published in the ANNALS under the headings "College News Notes" and "Obituaries."

This new publication, which is primarily for distribution to the members of The American College of Physicians, will contain all those personal notes concerning the College members, and those abstracts of the Proceedings of the Board of Governors and Board of Regents, which are of especial interest to the members of the College. In addition, there will appear, both in the BULLETIN and in the ANNALS, that portion of the present College News Notes containing announcements that concern all internists. In the ANNALS, such material will be published under the heading of "Medical News."

The first issue of the new BULLETIN will be published in February, 1960, and thereafter it will appear bimonthly. Dr. Thomas M. McMillan has accepted the editorship of the BULLETIN. The editorial office will be in close connection with the College headquarters.

THE PRESENT STATUS OF PERIPHERAL ARTERIAL RECONSTRUCTION FOR ARTERIOSCLEROSIS OBLITERANS

Some years ago when transurethral resection for prostatic obstruction was new, an article appeared titled "Transurethral Resection without the Moonlight and Roses," intended to place this then recent innovation in proper perspective. Operations to restore circulation in peripheral arteries occluded by arteriosclerotic disease have now been around long enough so that it should be possible to examine these new procedures objectively without "the moonlight and roses."

Blood vessel anastomosis was described by Alexis Carrel [1] in 1902. Arteriography and aortography were standardized by R. Dos Santos [2] in 1929. The development of these accurate diagnostic methods made feasible

[1] Carrel, Alexis: Direct anastomosis of blood vessels by end-to-end union, Lyon méd. **93**: 859, 1902.

[2] Dos Santos, R., Lamas, A. C., and Caldas, J. P.: Artéreographie des membres, de l'aorte et de ses branches abdominales, Bull. et mém. Soc. nat. de chir. **55**: 687, 1929.

the introduction of endarterectomy by J. C. Dos Santos [3] in 1947 and by Bazy [4] in France in 1949. Homologous arterial grafting was perfected by Gross [5] and his associates in 1948 for application to coarctation of the aorta. Vein grafts and homografts were soon thereafter applied to other types of arterial occlusions by Kunlin [6] in 1951, these methods rapidly gaining popularity in this country. During the past two or three years plastic prostheses (dacron [7] and teflon [8]) have almost completely taken the place of homografts. Vein grafts still have a limited usefulness,[9] while thromboendarterectomy, always popular on the Pacific coast,[10, 11] has had a recent vogue in other sections of the country as well.[12, 13] The method of end-to-side shunting [14, 15] has in general been found preferable to resection and replacement in occlusive disease.

The emphasis in this review will be on occlusive disease as contrasted with aneurysm, and on the peripheral ileo-femoro-popliteal vessels rather than the more central aorto-iliac system. Clinically this represents the essence of the major problem in peripheral arteriosclerosis obliterans. At its annual meeting in 1959, the American Medical Association awarded its medal of honor to Michael DeBakey of Houston, Texas for his contributions to vascular surgery. His accomplishments [16, 17] in the field of vascular reconstructive surgery have been vast and brilliant, but successes such as his

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tend to obscure the limited nature of the progress in the surgical management of the more distal peripheral arterial occlusions.

There are several reasons for the relative lack of success in occlusive disease of the more peripheral vessels. The requirement of adequate run-off has now been well established in arterial surgery.[18] Not only must new channels be provided, but the blood must have some place to go, or the new channels will more or less promptly become re-occluded. Although the proportion of segmental as contrasted with extensive occlusions of the femoral vessels has been unexpectedly high, the incidence of a localized occlusion and associated adequate run-off has, in our experience, proved to be disappointingly low. This has been particularly true in the large group of diabetics, where diffuse involvement of the small peripheral arteries is especially striking. The relatively large series of cases amenable to surgery accumulated in the vascular centers is not a true indication of the incidence of suitable cases in a general medical or surgical practice, or in a community general hospital accepting run-of-the-mill admissions.

An additional problem is the inherent tendency of smaller (femoral) as compared to larger (aorto-iliac) vessels to occlude in the presence of any imperfections in the channel, such as suture lines, small postoperative thrombi and residual areas of atherosclerosis. Homografts seem to have a particularly fatal tendency to undergo degenerative changes.[19] Last, but certainly not the least, is the progression of disease with consequent closing off of newly created shunts or existing collateral channels.[20]

Complicating the situation further is the common coexistence of other degenerative processes such as advanced coronary disease, cardiac insufficiency, renal disease or cerebrovascular problems. Attempting to determine the wisdom of performing a procedure of uncertain success in a patient with troublesome complications can indeed be very trying. There are most certainly circumstances where accepting the loss of an extremity, or more pertinently a troublesome intermittent claudication, may be wiser than subjecting a patient to a procedure of doubtful outcome.

Rob [21] of England has estimated that some 25% of patients with femoropopliteal occlusions are suitable for reconstruction. DeBakey [22] feels that this figure is low and estimates that in his experience the number of superficial femoral artery occlusions suitable for reconstruction would exceed 50%. It is difficult fully to explain this discrepancy in the findings of the

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[22] DeBakey, M. E.: Editorial Comment on preceding in Year Book of Surgery, 1957–1958 Series, p. 276, Year Book Publishers, Inc., Chicago, 1957.

two authorities, but the method of selection may certainly be a factor. The lower figure would much more nearly approximate conditions in this reviewer's community. Roberts and Hoffman [23] found that about 30% of patients hospitalized for possible amputation of the lower extremity were suitable for grafting procedures.

What is the fate of cases operated upon? Adequate long-term follow-up reports of significant size are difficult to find. Warren [24] reported on 70 patients with ileo-femoro-popliteal arterial reconstructions treated by three different methods: 36 by homografts, 13 by venous autografts, and 21 by thromboendarterectomy. The incidence of patency for at least one year after operation was 9% for homografts, 18% for venous autografts and 55% for thromboendarterectomy. Linton [25] reported that in 38 patients treated by by-pass homografts only 60% were patent in two to three years, while in 12 treated with plastic prostheses with initial success only one was still open two years later. In a follow-up study on 66 successful femoral homografts Szilagyi [19] reported that at the time of the study, 47 were open and 19 were closed. Of those still open, 24 were shown by arteriography to manifest varying degrees of structural degeneration. Butcher and Robinson [26] reported that of 19 patients having femoral artery homografts, postoperative thrombosis developed in seven, five had later serious complications, while seven were functioning 12 to 21 months postoperatively. Hohf and Laufman [27] reported nine early and 11 late failures in 33 ileo-femoral homografts, and six early and seven late failures in 23 nylon prostheses. These writers emphasized the importance of poor run-off in graft failures. Humphries [28] and his group reported follow-up studies on 438 cases of aorto-iliac and femoral homografts available for follow-up. In this group there were 70 late failures, but of these 70, 55 were in the femoro-popliteal group. The breakdown on the locations of the replacements in the 438 cases is not given. Humphries, however, has been one of the last to maintain confidence in the efficacy of homografts. Cannon [29] and his group have reported on 57 femoro-popliteal endarterectomies. Of 16 cases with good run-off, 13 had restoration of pulses for two to 56 months. Of the 13, however, three developed severe arteriosclerotic heart disease, and another three died

[23] Roberts, B., and Hoffman, D.: Arterial grafting in severely ischemic legs, J. A. M. A. **166**: 1316, 1958.

[24] Warren, R., and Villavicencio, J. L.: Ileofemoropopliteal arterial reconstructions for arteriosclerosis obliterans: factors influencing late patency, New England J. Med. **260**: 255, 1959.

[25] Linton, R. R.: Discussion of Ref. 16, at Meeting of American Surgical Association, April 16-18, 1958 at New York, N. Y., Ann. Surg. **148**: 340, 1958.

[26] Butcher, H. R., and Robinson, J. R.: Experiences with arterial grafting for major arterial occlusive disease, Am. J. Surg. **95**: 25, 1958.

[27] Hohf, R. P., Trippel, O. H., and Laufman, H.: Clinical comparison of homografts and braided nylon in arterial by-pass surgery, Arch. Surg. **77**: 552, 1958.

[28] Humphries, A. W., Hawk, W. A., DeWolfe, V. G., and LeFevre, F. A.: Clinicopathologic observations on the fate of arterial freeze-dried homografts, Surgery **45**: 59, 1959.

[29] Cannon, J. A., Barker, W. F., and Kawakami, I. G.: Femoral popliteal endarterectomy in treatment of obliterative atherosclerotic disease, Surgery **43**: 76, 1958.

suddenly of myocardial infarction in two to 33 months. Of 29 operations on 27 patients with impaired run-off, 14 had improved circulation for four to 63 months. In another 14 patients with poor run-off, no pulsations were restored, but two were considered to have been somewhat improved. Crawford [30] of DeBakey's group, where a dacron prosthesis is now used exclusively, reported that more than 80% of immediate good results in femoral occlusion had been maintained "for as long as" four years. In a recent report from that clinic [17] an operability rate of close to 60% is claimed. The operative mortality in their experience was about 0.5%. Occlusions recurred in about 15% "over a five year period." In over one-half of these, normal circulation was restored by a second operation, giving a final success rate of better than 90%. This striking success seems to stand almost alone.

In a recent compilation from the Central Artery Bank of the Chicago Heart Association,[31] 27 resection or by-pass grafts for peripheral occlusive disease were reported. Twenty of these thrombosed in periods up to 15 months. Six were functioning after periods of three to 36 months, while one case was lost to follow-up.

It must be concluded on the basis of present evidence that best results can be expected in by-pass shunts of micro-crimped dacron or teflon or in thromboendarterectomy, performed in cases with adequate run-off. Conditions suitable for surgery will be present in some 25 to 60% of cases. Immediate restoration of circulation can be expected in somewhere between 65 and 95% of operated cases, while late failure will occur in 10 to 80% of those having immediate success. The evidence is still equivocal, and the paucity of reports and the slowness with which they are appearing would suggest that success in this area is still of a limited nature.

S. J. Goldowsky, M.D.

[30] Crawford, E. S.: Arteriosclerotic occlusive disease, Heart Bulletin, p. 16, Jan.–Feb. 1958.

[31] Weinberg, M., Jr., Fell, E. H., deTakats, G., and McElwaine, N.: Use of homografts dispensed by Central Artery Bank of Chicago Heart Association, J. A. M. A. 170: 2132, 1959.

REVIEWS

The Functions of the Endocrine Glands. By PETER F. HALL, M.D., M.R.C.P., M.R.A.C.P. 290 pages; 22.5 × 14.5 cm. W. B. Saunders Company, Philadelphia. 1959. Price, $5.75.

The book opens with a chapter on the chemistry of hormones; present knowledge of chemical characteristics and structural formulae of hormones and their metabolic derivatives is presented. Single chapters are devoted to each endocrine gland; the embryology, histology, biochemistry and physiology of each hormone are discussed. Finally, there are chapters on the relationship between the central nervous system and the endocrine glands, and on steroid metabolism.

This book should be valuable to the undergraduate student and to the graduate who desires to obtain rapidly a concise knowledge of the physiology of the endocrine system. A detailed bibliography is not given, but the author does include references to recent review articles on each subject. The information presented is on the whole up to date and the illustrations and diagrams are good. The book is not intended to be a text of clinical endocrinology, and the sections on clinical aspects of endocrine disorders are only briefly mentioned. The book is not sufficiently detailed to be of interest to those who are concerned primarily with specialized knowledge in both basic and clinical aspects of endocrinology.

J. G. W.

Primer Symposium Internacional Sobre Fiebre Reumatica. 530 pages; 22.5 × 17.5 cm. Instituto Nacional de Cardiologia, Mexico, D. F. 1958.

In April 1956, The National Institute of Cardiology of Mexico sponsored the First International Symposium on Rheumatic Fever. A group of prominent investigators from Brazil, Canada, England, the United States and Mexico took active part in this symposium. Among others, Benedict Massell discussed the clinical and preventive aspects of rheumatic cardiopathies; E. G. Bywaters, the immunological aspects and Paul Klemperer the histopathogenesis of rheumatic fever. Edward Bland discussed aortic insufficiency in young adults. The Brazilian group presented original work on electrophoretic studies. The Mexican group among other topics discussed digitalis intoxication and the visceral lesions in rheumatic fever. Rheumatic pneumonitis and encephalopathy were emphasized. The latter topics are of particular importance because of the few reports available in the English literature. For an unknown reason, a severe encephalopathy, seldom seen in the North American continent or Europe is occasionally described in some of the Mexican cases. Once clinical evidence is noted, the prognosis is essentially poor. In the Mexican series, the mortality among cases of rheumatic encephalopathy is 43%. In 998 postmortem examinations on rheumatic heart disease patients, 11% had definite cerebral lesions.

The purpose of this book was to make available to a large number of physicians the wealth of information discussed at this symposium. I believe the goal has been accomplished. Like many good books, delay in publication is a drawback of this book. Twenty-seven months elapsed from the time the symposium was held to its date of publication. Nevertheless, the data collected in its 530 pages make available material of considerable value to persons concerned with problems of rheumatic fever and it is recommended as a source book.

LUIS FELIPE GONZALEZ, M.D.

Clinical Epidemiology (The Scientist's Library: Biology and Medicine, edited by PETER P. H. DE BRUYN, M.D.). By JOHN R. PAUL, M.D., Sc.D., Professor of Preventive Medicine, Yale University School of Medicine. 291 pages; 22 × 14.5 cm. The University of Chicago Press, Chicago, Ill. 1958. Price, $5.00.

Dr. Paul has prepared a very concise review of epidemiology for students and physicians. Epidemiology is presented as a science concerned with the circumstances under which people become ill. It is presented from the medical point of view and not as a statistical science. The text is divided into three parts, covering (1) definitions and concepts; (2) principles; and (3) sample diseases.

Drawing on his own vast experience as an epidemiologist and teacher, the author has produced a well written and interesting text which will be of value to students and practicing physicians.

G. E.

Strong and Elwyn's Human Neuroanatomy. 4th Ed. By RAYMOND C. TRUEX. 511 pages; 26 × 17.5 cm. The Williams and Wilkins Co., Baltimore. 1959. Price, $10.00.

This is the fourth edition of this neuroanatomy textbook which first appeared in 1943. The present edition preserves the orientation of the original edition, which was to present the anatomic material with its clinical uses in mind. This orientation is less evident in the present edition than it was in the original work; nevertheless, the anatomic features most important for clinical uses are given more space and stress. In other respects, this resembles the standard neuroanatomy text. It is complete, well illustrated, possesses a useful index and an extensive bibliography located at the end of the volume.

The book will be useful as a text for medical students, as well as a reference volume for the trainees in the neurologic sciences.

C. V. B.

A Clinical Introduction to Heart Disease. By CRIGHTON BRAMWELL, M.A., M.D., F.R.C.P. 229 pages; 22.5 × 14.5 cm. Oxford University Press, New York, N. Y. 1959. Price, $5.50.

The author's object is "to present the basic principles of cardiology," confining his "attention almost exclusively to problems in which the family doctor needs help, and to methods of treatment applicable in the patient's own home." The general practitioner constitutes the patient's first line of defense, and he should have available a maximum, rather than a minimum, of information. This volume does not provide him with the complete, concise and modern information he would require to discharge his responsibilities. The sections on therapy frequently omit significant recent advances and the sections on diagnosis are incomplete in many instances. Admonitions to reassure the patient occur repeatedly in the text, but specific recommendations for therapy to warrant this reassurance all too often are lacking.

If the practitioner and senior student, for whom this text is intended, were to depend upon it exclusively for specific details of diagnosis and therapy of the more common types of heart disease, the results would be unsatisfactory.

S. S.

Diagnosis of Congenital Heart Disease. 2nd Ed. By SVEN R. KJELBERG, M.D., EDGAR MANNHEIMER, M.D., ULF RUDHE, M.D., and BENDT JONSSON, M.D. 866 pages; 26.5 × 18.5 cm. The Year Book Publishers, Inc., Chicago. 1959. Price, $28.00.

This is the second edition of *Diagnosis of Congenital Heart Disease* which originally appeared in 1955. The present edition has retained the same excellent features, and has been considerably enhanced by a more extensive bibliography of 727 references and over 700 illustrations.

The same format has been maintained but four new chapters have been added and extensive changes made in most other chapters, particularly in the organization and content of the sections on atrial septal defects and anomalous drainage of pulmonary veins.

In this text are presented the diagnostic findings in detail of 742 cases of congenital heart disease, with emphasis on the anatomy, clinical features, roentgenologic examinations, electrokymography, electrocardiography, cardiac catheterizations, and angiocardiography. Only passing reference is made to dye dilution studies. The format is to be commended as is the uniform good quality of the illustrations, particularly the angiocardiograms and anatomic studies. Chapters are devoted to embryology, roentgenology, anatomy, and specific diagnostic technics in congenital lesions.

The authors and publishers have presented a valuable text based on the experience of the cardiologic team at the Karolinska Sjukhuset. It is highly recommended to roentgenologists, cardiologists, and students as one of the most valuable texts available on congenital heart disease.

L. S.

Applied Pharmacology (Clark). 9th Ed. By ANDREW WILSON, M.D., Ph.D., F.R.F.P.S., and H. O. SCHILD, M.D., Ph.D., D.Sc. 750 pages; 23 × 14.5 cm. Little, Brown and Co., Boston. 1959. Price, $10.00.

One welcomes the appearance of a new edition of this standard text in pharmacology. That the volume has gone into its ninth edition testifies to high esteem with which this book is held by pharmacologists. The same clarity of expression and felicity of diction which characterized the volume in its early editions prevail in the present edition.

The general plan of approach to the subject of pharmacology employed by the late Professor A. J. Clark has been retained in this edition. The treatise introduces the subject by a discussion of the action of drugs on cells, the application of pharmacologic procedures, the methods of administering drugs and a discussion of the fate of drugs in the body. The subsequent chapters of the book discuss the systems of the body and the drugs which act upon them. Examples are "The Pharmacology of the Central Nervous System," "The Pharmacology of the Circulation" and "The Pharmacology of the Respiration." In each of these 34 chapters a physiologic discussion of the function of the organ system precedes the action of drugs on the system. This approach to the action of drugs in the treatment of disease is an excellent one for the student of medicine.

Brevity is one of the characteristics of this text. Many of the American treatises on this subject are much more detailed, embrace many more drugs and are consequently two or three times larger than this text. For example less than three pages are devoted to the use of drugs in neoplastic disease.

This volume is strongly recommended by the reviewer as an authoritative and concise treatise embracing the essentials of the subject of pharmacology for medical students.

JOHN C. KRANTZ, JR.

A Stereoscopic Atlas of Human Anatomy. Section IV. The Thorax (in two volumes). Vol. I: View-Master Reels 113–122; Vol. II: View-Master Reels 123–132. By DAVID L. BASSETT, M.D., Professor of Anatomy, Stanford University, California. 290 pages, 140 views. 21.5 × 17 cm. (loose-leaf, leather bound). Sawyer's, Inc., Portland, Oregon. 1958. Price, $16.50.

This fourth section of Bassett's *Stereoscopic Atlas of Human Anatomy*, which covers the anatomy of the thorax, is another step toward the completion of a stereo color atlas that is one of the finest teaching aids in the field of human anatomy. The sections on the "Central Nervous System," "Head and Neck," and "Upper Extremity," have appeared earlier. The other sections are in preparation. As each succeeding section of the atlas appears, the set becomes more and more valuable. The present set on the anatomy of the thorax depicts sequential views of meticulous and well-planned dissections. The specimens are well chosen and well prepared.

The two volumes of drawings that accompany the 140 views of dissections of the thorax are essentially a system of labeling the structures seen in the stereo views of dissections. For the beginning student in anatomy, the Atlas will serve as a good means of supplementing and reviewing anatomy. The surgeon and the intern will find it a convenient way to review topographical anatomy.

This stereo atlas will prove a boon to everyone concerned with human anatomy who may need occasionally or frequently to review any specific aspect of the subject.

FRANK H. J. FIGGE

Vascular Surgery. By GEZA DE TAKATS, M.D., M.S., F.A.C.S. 726 pages; 25.5 × 17 cm. W. B. Saunders Company, Philadelphia. 1959. Price, $17.50.

This is a well organized and very well illustrated monograph on vascular surgery. Reference to cardiac surgery is wisely omitted, except in its relationship to surgery of the arterial and venous systems.

Fundamental concepts are stressed and an excellent chapter is devoted to the examination of the patient. This chapter is divided into two sections: (1) diagnostic procedures for those with limited equipment, and (2) diagnostic procedures for detailed studies, research and advancing knowledge. Special technics of examination and testing are described in adequate detail.

In addition to the usual arterial and venous lesions, space is devoted to the problems of lymphedema, tumors of the vascular system, neurovascular lesions and essential hypertension.

All the illustrations are clear and well identified. The book is well indexed and the cross-indexing is excellent.

This is a superior type of reference volume for the physician or medical student interested in vascular problems.

G. H. Y.

Recent Advances in Paediatrics. 2nd Ed. Edited by DOUGLAS GAIRDNER, M.A. (Cantab.), D. M. (Oxon.), F.R.C.P. 378 pages; 21 × 14 cm. Little, Brown and Co., Boston. 1958. Price, $9.50.

This volume is a collection of illustrated reviews by several authors on subjects of interest in pediatrics. It is not a catalogue of all the recent advances or all the articles published. Instead it is a collection of ideas, many of them newly published since the last edition of this series in 1954, others (as the bibliographies show) proposed in the nineteenth century. The 13 chapters deal with the circulation at birth, the blood in infancy, jaundice in the newborn, growth, hypothyroidism, spina bifida cystica, hydrocephalus, the nephrotic syndrome, tuberculosis, rheumatic fever,

deafness, and pyogenic osteitis. Each is written by a person keenly interested in his subject, and most chapters are very provocative. In fact it is hard to read the book without frequent pauses to consider the implications and possible applications of each new idea.

G. S. C.

Pediatric Profiles. Edited by BORDEN S. VEEDER, M.D. 267 pages; 26 × 17.5 cm. C. V. Mosby Company, St. Louis. 1957.

This book is a compilation of thirty short biographical sketches of those men who were recognized for their contributions and dedicated devotion to pediatrics at the time of its rapid growth in the United States from 1900 to 1950. These sketches appeared singly in various numbers of the *Journal of Pediatrics* between November 1954 and November 1957 and are restricted to those men who were nationally recognized and who are no longer living. It includes a few Europeans who influenced pediatrics in the United States.

Arranged in chronologic order according to birth date, the biographies are written by physicians who were closely acquainted with the individual, often as one of his students and later in a training position or clinical association.

These short but pithy sketches give an insight into the man himself and his outlook, but they are not by any means an exhaustive listing of his deeds, academic positions or achievements—nor are they intended to be.

This collection of reprints is recommended to those who wish to gain a glimpse of the personality and the philosophy of this group which was so instrumental in giving stature to the specialty of pediatrics and medicine in general.

K. H. W.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Acute Medical Syndromes and Emergencies: Diagnosis and Treatment. By ALBERT SALISBURY HYMAN, M.D., Associate Clinical Professor of Medicine, New York Medical College, New York, N. Y.; with the collaboration of SAMUEL WEISS, M.D., Professor of Gastroenterology Emeritus, New York Polyclinic Medical School, New York, N. Y.; GEORGE GUTTMAN ORNSTEIN, M.D., Associate Clinical Professor of Medicine, New York Medical College, New York, N. Y.; HOWARD F. ROOT, M.D., Medical Director, Joslin Clinic, Boston, Massachusetts; ANNA RUTH SPIEGELMAN, M.D., Assistant Professor Clinical Medicine, New York University Postgraduate Medical School, New York, N. Y.; and JACK ABRY, M.D., Associate Attending Physician, New York City Hospital, Elmhurst, N. Y. 442 pages; 21 × 14 cm. 1959. Lansberger Medical Books, Inc., New York. Price, $8.75.

Anatomy and Physiology. Vol. 2: Urinary, Respiratory, and Nervous Systems, Sensations and Sense Organs, Endocrine and Reproductive Systems. College Outline Series. By EDWIN B. STEEN, Ph.D., and ASHLEY MONTAGU, Ph.D. 314 pages; 21 × 13 cm. (paper-bound). 1959. Barnes & Noble, Inc., New York. Price, $2.50.

Atlas of Human Anatomy. 5th Ed. By FRANZ FROHSE, late of the University of Berlin; MAX BRÖDEL, late of Johns Hopkins University; and LEON SCHLOSSBERG, Johns Hopkins University. 5th Ed. (1959): Text by SAMUEL SMITH,

edited by M. F. Ashley Montagu; Section on Endocrine Glands by Charles F. Geschickter; illustrated by Leon Schlossberg; notes by Jesse M. Williams. 180 pages; 21 × 13.5 cm. (paper-bound). 1959. Barnes & Noble, Inc., New York. Price, $2.95; in cloth, $4.50.

Biopsy Manual. By James D. Hardy, M.D., Professor and Chairman of the Department of Surgery, University of Mississippi School of Medicine; James C. Griffin, Jr., M.D., Assistant Instructor in Surgery, Administrative Chief Resident in Surgery, National Cancer Institute Trainee, University of Mississippi School of Medicine; and Jorge A. Rodriguez, M.D., Assistant Professor of Surgical Anatomy, The Department of Surgery, University of Mississippi School of Medicine. 150 pages; 26 × 17.5 cm. 1959. W. B. Saunders Company, Philadelphia. Price, $6.50.

Current Medical References. Edited by Paul J. Sanazaro, M.D., Associate Professor of Medicine, University of California School of Medicine, San Francisco, California. 535 pages; 18 × 10 cm. (paper-bound). 1959. Lange Medical Publications, Los Altos, California. Price, $3.50.

The Diabetic's Handbook. 2nd Ed. By Anthony M. Sindoni, Jr., M.D., Chief of the Department of Metabolism, St. Joseph and Philadelphia General Hospitals, etc.; with 18 collaborators; foreword by Charles C. Wolferth, M.D., Emeritus Professor of Medicine, University of Pennsylvania School of Medicine; prologue by Isidor S. Ravdin, M.D., John Rhea Barton Professor of Surgery, and Director, Harrison Department of Surgical Research, University of Pennsylvania School of Medicine; introduction by Hugh L. C. Wilkerson, M.D., Medical Director, U. S. Public Health Service, etc. 285 pages; 21 × 14 cm. 1959. The Ronald Press Company, New York. Price, $4.50.

The Fluids of Parenteral Body Cavities. Modern Medical Monograph 19. (Editor in Chief: Irving S. Wright, M.D.; Consulting Editor: Richard H. Orr, M.D.) By Paul D. Hoeprich, M.D., Assistant Professor of Medicine and Assistant Research Professor of Pathology, University of Utah College of Medicine, Salt Lake City, Utah; and John R. Ward, M.D., Assistant Professor of Medicine, University of Utah College of Medicine, Salt Lake City, Utah. 98 pages; 22.5 × 14 cm. 1959. Grune & Stratton, New York. Price, $4.75.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. 4th Ed. By Philip Lewin, M.D., F.A.C.S., F.I.C.S., Professor Emeritus of Bone and Joint Surgery, and Formerly Head of Department, Northwestern University Medical School, etc.; special drawings by Harold Laufman, M.D., F.A.C.S., Associate Professor of Surgery, Northwestern University Medical School, etc. 612 pages; 24 × 16 cm. 1959. Lea & Febiger, Philadelphia. Price, $14.00.

Handbook of Circulation. Analysis and Compilation by Philip L. Altman; edited by Dorothy S. Dittmer and Rudolph M. Grebe; prepared under the direction of the Committee on the Handbook of Biological Data, Division of Biology and Agriculture, National Academy of Sciences, National Research Council. 393 pages; 28 × 21.5 cm. (flexible cover). 1959. W. B. Saunders Company, Philadelphia. Price, $7.50.

Handbook of Poisoning: Diagnosis and Treatment. 2nd Ed. By Robert H. Dreisbach, M.D., Ph.D., Professor of Pharmacology, Stanford University School of Medicine, Stanford, California. 474 pages; 18 × 10 cm. (paper-bound). 1959. Lange Medical Publications, Los Altos, California. Price, $3.50.

Hearing Loss: What Can Be Done About It. Keystone Book KB11. By GREYDON G. BOYD, M.D., Associate Clinical Professor of Otorhinolaryngology, New York-Bellevue Medical School, etc.: illustrations by A. G. PECK. 190 pages; 18.5 × 11 cm. (paper-bound). 1959. J. B. Lippincott Company, Philadelphia. Price, $1.45.

High Blood Pressure. Keystone Book KB12. By EUGENE B. MOZES, M. D.; drawings by ROY HEARN. 192 pages; 18.5 × 11 cm. (paper-bound). 1959. J. B. Lippincott Company, Philadelphia. Price, $1.45.

Human Nutrition and Dietetics. By SIR STANLEY DAVIDSON, B. A. Cantab., M.D., F.R.C.P.Ed., F.R.C.P.Lond., M.D.Oslo, Physician to Her Majesty the Queen in Scotland, etc.; A. P. MEIKLEJOHN, M.A., B.Sc., D.M.Oxon., M.R.C.P.Lond., Lecturer in Nutrition, University of Edinburgh, etc.; and R. PASSMORE, M.A., D.M.Oxon., Reader in Physiology, University of Edinburgh, etc.; with a foreword by LORD BOYD ORR, D.S.O., M.C., LL.D., F.R.S., formerly Director-General, Food and Agriculture Organisation of the United Nations. 844 pages; 25.5 × 16 cm. 1959. The Williams & Wilkins Co., Baltimore, exclusive U. S. Agents. Price, $15.00.

The Megaloblastic Anemias. Modern Medical Monographs 18. (Editor in Chief: IRVING S. WRIGHT, M.D.; Consulting Editor: RICHARD H. ORR, M.D.) By VICTOR HERBERT, M. D., Research Assistant in Hematology, The Mount Sinai Hospital, New York, etc. 162 pages; 22.5 × 14 cm. 1959. Grune & Stratton, New York. Price, $6.00.

Pain and Itch: Nervous Mechanisms. Ciba Foundation Study Group No. 1. In honour of PROF. MED. DR. Y. ZOTTERMAN, M.D., R.V.O. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P.; and MAEVE O'CONNOR, B.A. 120 pages; 19 × 12.5 cm. 1959. Little, Brown and Company, Boston. Price, $2.50.

Pharmacopoea Internationalis. 1st Ed. Supplement. 224 pages; 24.5 × 17 cm. 1959. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, New York. Price, $5.00.

The Physician and the Law. 2nd Ed. By ROWLAND H. LONG, Member Massachusetts and New York Bars, etc.; foreword by MILTON HELPERN, M.D., Chief Medical Examiner, New York City. 302 pages; 21.5 × 14 cm. 1959. Appleton-Century-Crofts, Inc., New York. Price, $5.95.

The Preparation of Medical Literature. By LOUISE MONTGOMERY CROSS, M.A.; with a chapter, *Charts and Graphs,* by SHIRLEY BATY, Medical Illustrator, The Memorial Center for Cancer and Allied Diseases. 451 pages; 23.5 × 16 cm. 1959. J. B. Lippincott Company, Philadelphia. Price, $10.00.

Steric Course of Microbiological Reactions. Ciba Foundation Study Group No. 2. In honour of PROF. DR. V. PRELOG. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P.; and CECILIA M. O'CONNOR, B.Sc. 115 pages; 19 × 13 cm. 1959. Little, Brown and Company, Boston. Price, $2.50.

Tumors of the Pancreas. (*Atlas of Tumor Pathology, Section VII—Fascicles 27 and 28.*) By VIRGINIA KNEELAND FRANTZ, M.D., Professor of Surgery, College of Physicians & Surgeons, Columbia University, etc. 149 pages; 26 × 20 cm. (paper-bound). 1959. Published by the Armed Forces Institute of Pathology

under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council, Washington, D. C. For sale by the American Registry of Pathology, Armed Forces Institute of Pathology, Washington 25, D. C., at $1.50.

Upper Digestive Tract. The Ciba Collection of Medical Illustrations. Part I of Volume 3: *A Compilation of Paintings on the Normal and Pathologic Anatomy of the Digestive System.* Prepared by FRANK H. NETTER, M.D.; edited by ERNST OPPENHEIMER, M.D.; commissioned and published by CIBA. 206 pages; 32 × 24 cm. 1959. Ciba Pharmaceutical Products, Inc., Summit, New Jersey. Price, $12.50.

Work and the Heart: Transactions of the First Wisconsin Conference on Work and the Heart. By 93 authors. Edited by FRANCIS F. ROSENBAUM, M.D., Associate Clinical Professor of Medicine, Marquette University School of Medicine; and ELSTON L. BELKNAP, M.D., Professor and Director, Department of Occupational and Environmental Medicine, Marquette University School of Medicine. 537 pages; 26.5 × 19 cm. 1959. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $12.00.

MEDICAL NEWS

Meetings—*National*

American College of Radiology, Roosevelt Hotel, New Orleans, Feb. 3–6. Mr. William C. Stronach, 20 N. Wacker Dr., Chicago 6, Executive Director.

American Gastroenterological Association, Roosevelt Hotel, New Orleans, March 31–April 2. Wade Volwiler, M.D., Department of Medicine, University of Washington, Seattle, Secretary.

American Psychosomatic Society, Sheraton-Mount Royal Hotel, Montreal, March 26–27. Miss Joan K. Erpf, 265 Nassau Road, Roosevelt, N. Y., Executive Assistant.

American Society of Internal Medicine, The Palace Hotel, San Francisco, April 1–3. Mr. Robert L. Richards, 350 Post Street, San Francisco 8, Executive Director.

American College of Cardiology, Indianapolis, May. Philip Reichert, M.D., 2709 Empire State Bldg., New York 1, Executive Director.

American Federation for Clinical Research, Chalfonte-Haddon Hall, Atlantic City, N. J., May 2. Mr. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.

American Pediatric Society, New Ocean House, Swampscott, Mass., May 5–6. Aims C. McGuinness, M.D., 2800 Quebec St., N. W., Washington 8, D. C., Secretary-Treasurer.

American Psychiatric Association, Inc., Hotel Traymore, Atlantic City, N. J., May 9–13. C. H. Hardin Branch, M.D., 156 Westminster Ave., Salt Lake City 15, Utah, Secretary.

American Society for Clinical Investigation, Haddon Hall, Atlantic City, N. J., May 1–2. Saul J. Farber, M.D., N.Y.U. College of Medicine, 550 First Ave., New York 16, Secretary.

Association of American Physicians, Haddon Hall, Atlantic City, N. J., May 3–4. Paul B. Beeson, M.D., Yale University School of Medicine, New Haven 11, Conn., Secretary.

Meetings—*International*

First Bahamas Allergy Conference, Nassau Beach Lodge, Nassau, Bahamas, March 5–12. B. L. Frank, M.D., P. O. Box 4037, Fort Lauderdale, Fla., Organizing Physician.

International Symposium on "The Blood Platelets," Henry Ford Hospital, Detroit, March 17–19. Shirley A. Johnson, Ph.D., Henry Ford Hospital, Detroit 2, Chairman.

Association of National European and Mediterranean Societies of Gastro-Enterology (Asnemge), 6th Congress, Leiden, Netherlands, April 20–24. For information write: ASNEMGE, 22, avenue d'Amerique, Anvers, Belgium.

Bahamas Medical Conference, British Colonial Hotel, Nassau, April 1–14. For information write: B. L. Frank, M.D., P. O. Box 4037, Fort Lauderdale, Fla.

International Academy of Pathology, Memphis, Tenn., April 25–27. For information write: F. K. Mostofi, M.D., Armed Forces Institute of Pathology, Washington, D. C.

International Conference of Cancer Cytology, Mexico City, May 2–11. Robert Nesbitt, M.D., Union University, Albany, N. Y., Secretary, U. S. Office.

Pan American Medical Association Congress, Mexico City, May 2–11. Joseph J. Eller, M.D., 745 Fifth Ave., New York 22, Director General.

Certifying Board Examinations

American Board of Internal Medicine: Oral Examination, San Francisco, March 30–31, April 1, 1960. Closing date for acceptance of applications for eligible candidates was January 2, 1960. Oral Examination, New York City, November 14, 15, 16, 17, 1960. Closing date for acceptance of applications for eligible candidates is July 1, 1960. Secretary-Treasurer, Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Preventive Medicine: Occupational Medicine Examinations will be given April 22, 23 and 24, 1960 in Rochester, N. Y., at a place to be determined. The Public Health Examinations will be given on a regional basis at the various Schools of Public Health some time during the month of April, 1960. Aviation Medicine Examinations will be published later. Secretary-Treasurer, Dr. Tom F. Whayne, 3438 Walnut Street, Philadelphia 4, Pa.

American Board of Physical Medicine and Rehabilitation: Oral and Written, New York, June 17–18, 1960. Secretary, Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Psychiatry and Neurology: San Francisco, March 14–15, 1960. Secretary, Dr. David A. Boyd, 103–110 Second Ave., S.W., Rochester, Minn.

The World Federation of Neurology

The World Federation of Neurology (WFN), international group representing neurology societies in 42 nations, announced world wide reporting of advances in the field of neurological associations through its official medical journal, *World Neurology*.

Scheduled for monthly publication, beginning July, 1960, *World Neurology* will be printed in four languages. The journal will be published by Lancet Publications, Minneapolis, Minn. Editor-in-Chief is Dr. Charles M. Poser.

Residencies in Cardiology

Two approved Residencies in Cardiology, beginning in July, 1960, are being offered at the City of Hope Medical Center, Duarte, Calif. The Residencies will emphasize clinical aspects of diagnosis and treatment of heart disease, and will provide training in technics of physiologic investigation of patients with cardiovascular disorders.

Candidates must be graduates of approved medical schools and should have completed at least one year of residency training in internal medicine. Residencies are for a period of one year, with a salary stipend of $4800.

Correspondence should be addressed to B. J. Allenstein, M.D., Acting Chief, Department of Cardiology, City of Hope Medical Center, Duarte, Calif.

Fellowships—Arthritis and Related Diseases

The National Foundation announces the availability of fellowships in the study of arthritis and related diseases.

Only physicians, licensed, who have had at least two years of specialty training acceptable to the appropriate American Board, are eligible. The candidate should propose a program of full time study in a hospital—preferably university-affiliated. The major portion of his time should be spent in clinical service, but a small amount should be devoted to research and teaching. Fellowships are awarded for a minimum

of one year, but may be renewed upon approval by the National Foundation's Clinical Fellowship Committee.

Financial support for the Fellow is $4500 a year, with $540 allowed annually for each dependent. Annual increases of $480 are ordinarily granted. For a full academic program, complete tuition and fees are paid; for other programs, a sum not to exceed $1250 including tuition, may be arranged.

Applications for consideration approximately May 1, 1960, must be received by February 1; for November 1, 1960, August 1; for February 1, 1961, November 1.

For further information, write to Division of Scholarships and Fellowships, Department of Professional Education, The National Foundation, 800 Second Avenue, New York 17, N. Y.

Colloquy on Advances in Medicine

The Third Annual Oklahoma Colloquy on Advances in Medicine will be March 24–26, 1960, at the University of Oklahoma Medical Center, Oklahoma City, with a program devoted to the adrenal steroids.

Fifteen guest lecturers and thirteen members of the Medical Center faculty will present papers dealing with the basic physiological and biochemical aspects of adrenal steroids. The pharmacology and side effects will be discussed.

For further information, write to the office of Postgraduate Education, University of Oklahoma Medical Center, 801 NE 13, Oklahoma City, Okla.

The Hugh Jackson Morgan Visiting Professorship of Medicine

Former house officers and friends of Dr. Hugh J. Morgan, M.A.C.P., Past President of the College, are establishing a fund which will support the Hugh Jackson Morgan Visiting Professorship of Medicine in the Department of Medicine at the Vanderbilt University School of Medicine. One of Dr. Morgan's outstanding qualities was his teaching ability at the bedside where, with the patient, students, house officers and other physicians, his brilliant and lucid comments brought about a stimulating exchange of medical information. It is proposed through this Visiting Professorship to stimulate and extend this type of bedside teaching by a physician chosen for his skills in clinical teaching who is to spend a week in residence at Vanderbilt.

Anyone who may wish to have a part in the establishment of this Visiting Professorship may do so by mailing a check to Miss Laura Thomas, Secretary, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

The most recent Immunization Information for International Travel may be obtained from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., at thirty cents a copy.

American Society of Internal Medicine

On Saturday, October 30, 1959, the Board of Trustees of the American Society of Internal Medicine met with representatives of the Health Insurance Council in Omaha, Nebraska, to discuss the many facets of health insurance contracts and how they affect the practice of Internal Medicine. Dr. Clark C. Goss, President of ASIM, and Mr. E. J. Faulkner, President of the Health Insurance Council, co-presided the

session at which approximately 50 persons were in attendance, including representatives of ten component societies of the American Society of Internal Medicine; members of the ACP Liaison Committee, Dr. Robert Wilson and Dr. Kenneth G. Kohlstaedt; Dr. Joseph D. McCarthy, Regent of the A.C.P. and Dr. Edmond M. Walsh, Governor of Nebraska for A.C.P.

All present agreed that the meeting was eminently successful in establishing mutual understanding between the two groups so that the future development of health insurance will contain provision for payment for the services of specialists in Internal Medicine.

A complete report on this session will be provided to the Officers of component societies so that they will know of the specific areas which were discussed and in turn be able to discuss them with their State Health Insurance Council representatives.

The same day the Board of Trustees met with representatives of the ten component societies and discussed their activities with particular respect to organization of their offices, committee programs and development of fee schedules within their areas.

FUTURE A.C.P. ANNUAL SESSIONS

1960, April 4–8	San Francisco, Calif.
1961, May 8–12	Bal Harbour, Fla.
1962, April 9–13	Philadelphia, Pa.
1963, April 1–5	Denver, Colo.
1964, April 6–10	Atlantic City, N. J.

Temple University, Philadelphia, Pa., has announced that the School of Medicine will build a seven to nine story Medical Research Building at a cost of four million dollars. This construction has been made possible by a grant of $1,437,750 from the National Institutes of Health. The new building will be in the area of the Medical School.

ANNOUNCEMENT

The Forty-first Annual Session of the American College of Physicians will be held in San Francisco, California, April 4–8, 1960. An outstanding scientific program has been arranged. Morning lectures, hospital clinics and panels offer practical, useful information each morning. Afternoon sessions will be divided between clinical, clinical investigation and basic science programs. All scientific sessions and an excellent technical exhibit will be at the Civic Auditorium.

All College members are cordially invited to attend the meeting of the American Society of Internal Medicine at the Sheraton-Palace Hotel, April 1–3, 1960. Headquarters for the College will be at the Mark Hopkins and Fairmont Hotels where all rooms are reserved for Officers, Regents and Governors of the College and for guest speakers. Reservations at numerous other good hotels may be made through the A.C.P.–A.S.I.M. Housing Bureau. Reservation forms are now available through the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

With a deserved reputation for hospitality, our San Francisco members have arranged for a variety of entertainment in this beautiful city. In this issue of the ANNALS there follows a description of some of their plans. The official program will appear in the February ANNALS. Make your plans now to attend what promises to be one of our best meetings.

View of downtown San Francisco with City Hall and Civic Plaza in foreground; background, San Francisco-Oakland Bay Bridge.

SAN FRANCISCO—YOUR 1960 HOST CITY

San Francisco's attraction for the medical profession is evidenced by the fact that most of the major medical groups have chosen the "City by the Golden Gate" for their annual meetings at one time or another.

One factor contributing to the city's popularity as a leading convention city is the fact the city-county administration, the hotels and motels, restaurants, night clubs and transportation companies work to make the city a good host to conventions—certainly one of the reasons for the decision of the Regents of the American College of Physicians to return to San Francisco in 1960, for the first time since 1948.

San Francisco provides living accommodations within a relatively compact area, with hotels, all manner of stores, smart shops, theatres, the Civic Auditorium with underground Brooks Hall adjoining, the new California Masonic Memorial Temple atop Nob Hill and the city's many fine restaurants within a small area.

Within the six by seven mile limits of the city-county boundaries are such attractions for off-convention hours as the famed Cliff House and Seal Rocks and nearby Playland at the Beach and Fleishhacker Zoological Gardens; such historic landmarks as the San Francisco Presidio and old Mission Dolores, founded in 1776; Fisherman's Wharf and its seafood restaurants; the famed Embarcadero where ships from around the world discharge and load cargoes. The city's famed cable cars also merit an off-convention-time ride, rising as they do across the city's major hills, affording panoramic views of the city and the Bay, and the two great bridges—the Golden Gate Bridge, second longest single-suspension span, and the massive San Francisco-Oakland Bay Bridge.

One of San Francisco's cable cars gives its passengers a good view of Alcatraz and the Bay, with the hills of Marin County beyond.

San Francisco's changing downtown skyline has been handsomely adorned by the new headquarters building of the Crown-Zellerbach Corporation; barely visible in the lower left of the photo is a new branch of the American Trust Company—a completely circular, glass enclosed branch bank.

San Francisco's fabulous China Town, largest outside the Orient.

Other spare-time attractions include Golden Gate Park, one of the most famous and handsome parks in the world where vistors may enjoy the California Academy of Sciences—oldest scientific foundation in the West—Steinhart Aquarium; Morrison Planetarium; the recently dedicated Eastwood Hall of Botany; M. H. de Young Memorial Museum; the Japanese Tea Garden, relic of the 1894 mid-winter fair; Chinatown, oldest and largest outside the Orient with its teeming streets, quaint shops and Oriental atmosphere; and Montgomery Street, "Wall Street of the West," from which industries and businesses around the world are directed and financed.

The city's famous shopping "Triangle" is noted for some of the most unusual and distinguished shops and stores to be found anywhere in the United States.

Nearby points of interest are Muir Woods National Monument, where giant redwood trees form a natural cathedral grove; important wine growing areas where some of California's finest wines are produced; the Monterey Peninsula and Carmel by the Sea, and many others.

San Francisco's temperate, year-round climate, with an occasional touch of fog, makes it an ideal convention and vacation city.

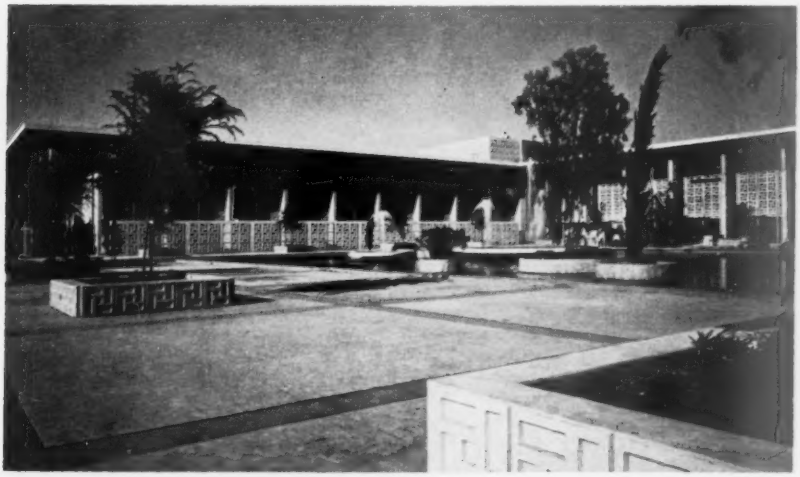
San Francisco's famed Bay Bridge, the world's longest and costliest (8¼ miles in length).

Fisherman's wharf—San Francisco, small blue ships anchored at the dock after a day's haul. Restaurants alongside serve delicious fish dishes.

For the medical man, San Francisco has equally interesting aspects. Almost from the days of the 1849 Gold Rush the city has been the Nation's Western medical center. By one estimate, one in every 300 Gold Rush immigrants was a doctor and the total of physicians coming to California at that time may have totaled about 1500. As some one said, doctors had no immunity to gold fever. Most of them had their try at the gold fields, then went back to the settlements and again took up their own calling.

Soon, two schools of medicine were established in San Francisco and the banner of Western medical leadership was firmly planted there. A century has elapsed since then and the banner is still there.

Since the last meeting of the American College of Physicians in San Francisco in 1948, one of the two medical schools which adorned the city for almost a century has moved to nearby Palo Alto.



PATIENT'S-EYE VIEW OF THE NEW STANFORD MEDICAL CENTER
All patient-rooms face the outside of the building, hence this is the view available to most patients at the Stanford Medical Center. The Center will be dedicated September 17–18.

Stanford University Medical School and the University's School of Nursing have been integrated with their parent institution, Stanford University, on the campus of the University near Palo Alto, 30 miles to the South.

The new Medical School facilities occupy four buildings in the Center. These buildings, erected at a cost of $9,300,000, are the Boswell Building, which contains a majority of the clinical facilities; the Medical School Building; the Lane Building, which houses the 165,000-volume Lane Medical Library—largest collection in the Western United States; and the Edwards Building in which rehabilitation services are housed.

Special equipment unique to the new Stanford Medical School includes a medical linear accelerator, a six-million electron volt "baby" atom smasher for deep X-ray therapy; artificial kidney; artificial heart-lung; cine radiography unit and isotope therapy laboratory.

Related University facilities include high-energy electron accelerators; X-ray microscopy; computer laboratory and a nuclear magnetic resonance spectrometer.

Aerial view of the University of California Medical Center, San Francisco. Principal buildings include (see key on overlay): (1) Langley Porter Neuropsychiatric Institute; (2) Herbert C. Moffitt Hospital; (3) Medical Sciences Building; (4) Clinics Building; (5) old University of California Hospital, now being remodeled; (6) Guy S. Millberry Union. Building (7) in rear, completed in 1897, is one of the original structures on the San Francisco campus—the old Medical School Building.

Meanwhile, the San Francisco Stanford Hospital is continuing to operate under University supervision while its future is determined.

The University of California Medical Center in San Francisco is in the midst of an exciting expansion of plant and services which, more than ever, make the city "the pivot of medicine in the Western United States."

The University of California is now the world's largest university. It is recognized everywhere as one of the world's greatest. The San Francisco Medical Center is one of its eight campuses and the only one devoted entirely to the health sciences and their relationship to man and his environment.

It is unique in being one of the few centers in the Nation housing, on a single campus, Schools of Medicine, Pharmacy, Dentistry and Nursing.

The most striking element of the new facilities at the Medical Center is the 16-story, 474-bed Herbert C. Moffitt Hospital, named for a former beloved and highly respected Dean and Professor of Medicine of the School of Medicine. Adjacent is the Medical Sciences Building. Both have been completed since 1954. The Medical Sciences Building contains a majority of the classrooms and teaching laboratories, the 135,000-volume medical library, the deans' offices of the four Schools and many research facilities.

The Clinics Building, adjoining the Medical Sciences Building, is occupied chiefly by the out-patient clinics of the Schools of Medicine and Dentistry.

The original University of California Hospital is undergoing renovation by stages and, when this program is completed, will provide a total of 210 additional beds at the Medical Center.

The Herbert C. Moffitt Hospital is, however, the major focus of interest at the Center.

The tenth floor of the Hospital, built with a $1,000,000 grant from the United States Public Health Service, houses the clinical area of the Cancer Research Institute. The 13th floor houses the Cardiovascular Research Institute, also supported by the U. S. Public Health Service.

In an isolated building, located in a two-story room with walls three feet thick, is the University's 70-million volt synchrotron, one of the largest in the world adapted for medical use. This Radiological Laboratory was built and is operated under a contract with the Atomic Energy Commission for experimental treatment of cancer.

Among the Medical Center's other research and teaching activities is the Langley Porter Neuropsychiatric Institute, a special research and teaching hospital of 108 beds, with associated laboratories and clinics. It is jointly staffed by the California Department of Mental Hygiene and the University.

Other research programs include the Francis I. Proctor Foundation for Research in Ophthalmology; the Metabolic Unit for Arthritis and Allied Diseases; and the Surgical Research Laboratories.

In addition to the University hospitals, there are 27 other hospitals in San Francisco. Of these, 22 are private and five are governmental.

The largest hospital in the city is the Letterman Army Hospital, one of the largest army hospitals in the United States. Located in the Presidio of San Francisco, it has 979 beds.

While the Navy does not have a hospital in San Francisco, it has a large general hospital across the Bay in Oakland. This is the U. S. Naval Hospital (Oak Knoll). It has 1,150 beds.

San Francisco General Hospital, with 944 beds and Laguna Honda Home, a custodial institution caring for nearly 2,000 patients with a total of 974 hospital beds, are next in size. They are operated by the Department of Public Health for the indigent ill and disabled.

Practically every seaport city has a United States Public Health Service Hospital and San Francisco is no exception. Its U.S.P.H.S. Hospital is well-staffed, accredited for the training of internes and residents and has 436 beds.

The Veterans Administration maintains in San Francisco a 405-bed hospital for general medical and surgical cases. Several other Veterans Administration hospitals for specialized services are located elsewhere in the San Francisco Bay area.

Of the private hospitals in San Francisco, Southern Pacific Hospital, maintained by the Southern Pacific Railroad for the care of the thousands of employees of its far-flung system, is the largest, having 450 beds. It is a diagnostic center for medical problems and has complete services in all the specialties.

Mt. Zion Hospital, operated by the Federated Jewish Charities of San Francisco, is the largest of the acute general hospitals in San Francisco, having 351 beds. It has been expanded rapidly in size and service since the College met in San Francisco in 1948, when it had about 150 beds.

There are four important hospitals operated by Sisters of Catholic Orders in San Francisco. St. Mary's Hospital, oldest Catholic Hospital in California, was founded by the Sisters of Mercy in 1857. It has 348 beds. St. Joseph's Hospital, operated by the Franciscan Sisters of the Sacred Heart, has 215 beds. Mary's Help Hospital, conducted by the Sisters of Charity of St. Vincent de Paul, has 179 beds and has one of the largest out-patient clinics in the city, exclusive of the University hospitals. Notre Dame Hospital, formerly Dante Sanitarium, is operated by the Sisters of Mercy. It has 170 beds.

Two hospitals, the French and Franklin, were built and operated by the French and German Benevolent Societies, respectively. The former has 196 beds and the latter 240 beds. Both have extensive remodeling plans on the drawing boards at the present time.

St. Luke's Hospital, operated under the auspices of the Episcopal Diocese of California, has 235 beds.

St. Francis Memorial Hospital, formerly a proprietary hospital, has undergone almost complete modernization with considerable enlargement and addition of services in recent years. It has 333 beds.

Children's Hospital, as its name implies, was founded primarily to provide child and maternal care but now also admits general patients. It has 237 beds.

Hahnemann Hospital, across the street from Children's, is one of the city's smaller general hospitals with 79 beds.

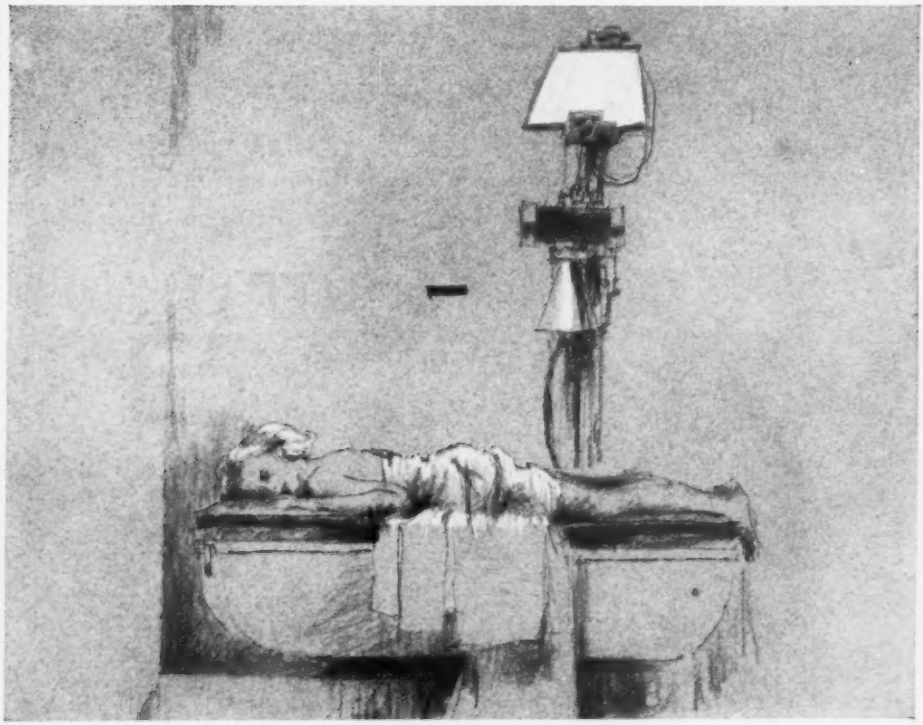
Kaiser Foundation also has a hospital in San Francisco with a capacity of 216 beds.

With one of the largest populations of Chinese and Chinese-Americans in the Nation, it is not surprising that San Francisco has a Chinese Hospital. Located in Chinatown, it has 56 beds.

New San Francisco Medical Society Headquarters

San Francisco has a vigorous Medical Society with about 1,700 active members. Organized in 1870, it now occupies a fine headquarters building, built to the Society's own specifications and occupied by it in 1955. The building is centrally located, has a large auditorium and other meeting rooms, a library, and catering facilities. It also houses the Irwin Memorial Blood Bank of the Medical Society.

Truly, San Francisco is, as has been said, a "pivot of medicine in the Western United States" and as such is happy to welcome once again the officers, members and guests of the American College of Physicians for their Forty-First Annual Session.



Nilevar® Combats Osteoporosis in Menopause or Hypercorticism

Since osteoporosis is a disease not of calcium deficiency but primarily of deficient formation of the protein bone matrix[1], the protein-building action of Nilevar (brand of norethandrolone) provides a rational and highly useful means of promoting osteogenesis.

Typically, subjective symptoms such as backache disappear promptly in osteoporotic patients treated with Nilevar. Objectively, the anabolic effects of the drug may be measured in the lessened excretion of nitrogen, calcium, potassium and phosphorus.

These actions appear to be equally effective[2-5] whether the osteoporosis originates in the postmenopausal or senile metabolic deficiencies of women or in the catabolic reaction to extended treatment with corticosteroids.

An initial adult dosage of 10 mg. three times a day may be continued for two or three weeks and then reduced in accordance with the response of the patient. Single courses of continuous treatment should not exceed three months, but may be resumed after a rest period of one month.

Nilevar is supplied as tablets, for oral dosage, of 10 mg. each and as ampuls of 1 cc. for intramuscular injection, each ampul containing 25 mg. of the drug in sesame oil and 10 per cent of benzyl alcohol by volume.

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Research in the Service of Medicine.

1. Ibarra, J. D., Jr.: Texas J. Med. 52:20 (Jan.) 1956. 2. Spencer, H., and Others: J. Clin. Endocrinol. 17:975 (Aug.) 1957. 3. Snapper, I.: Bone Diseases in Medical Practice, New York, Grune & Stratton, Inc., 1957, p. 18. 4. Spurr, C. L., and Others: GP 15:105 (May) 1957. 5. Editorial: Tissue Building and Protein Anabolizers, Brit. M. J. 2:785 (Sept. 27) 1958.

Whatever the indication,*
whatever degree of sedation desired
. . . a form of **Nembutal** will meet the need
(Nothing faster, shorter-acting, safer in barbiturate therapy.)

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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When the distraction is intestinal . . .

Motion study of the man in the second row rightly but sadly speaks of diarrhea. And yet intestinal repose could be his lot with POLYMAGMA. For POLYMAGMA contains Claysorb, which is more than five times as adsorptive as kaolin. It enlists two antibiotics working synergistically. It permits a low-dose regimen with high effectiveness. And it has a taste and texture that wear well all through treatment.

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300 mg CAPSULES

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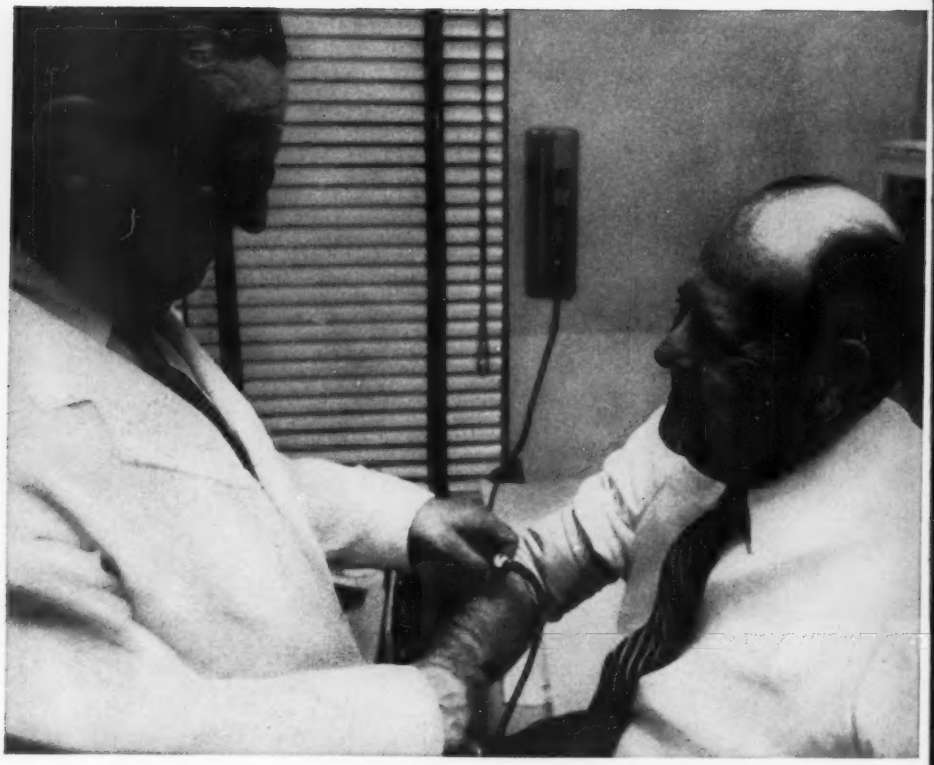
Why so many hypertensive patients prefer **Singoserp:**



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Almost all side effects relieved when Singoserp was substituted for other rauwolfia derivatives in 24 patients[2]

Side Effects	Incidence with Prior Rauwolfia Agent	Relieved by Singoserp	Not Relieved*
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Lethargy or fatigue	5	5	0
Nasal congestion	7	7	0
Gastrointestinal disturbances	2	0	2
Conjunctivitis	1	1	0

*Two of the 24 patients had two troublesome side effects.

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(syrosingopine CIBA)

First drug to try in new hypertensive patients

First drug to add in hypertensive patients already on medication

Supplied: Singoserp *Tablets*, 1 mg. (white, scored); bottles of 100.

1. Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. *169*:1609 (April 4) 1959.
2. Bartels, C. C.: N. E. J. Med. *261*:785 (Oct. 15) 1959.

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HIGH-DOSAGE NICOTINIC ACID EFFECTIVELY LOWERS CHOLESTEROL LEVELS

WITHOUT DIETARY RESTRICTIONS[1,2]

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In a recent report[1] on 44 patients, VASTRAN FORTÉ reduced plasma cholesterol levels to normal in 21 patients and lowered cholesterol levels by at least 40% in 14 more patients during a 30-week period. *There was no change in diet.*

VASTRAN FORTÉ produces no significant side effects on long-term administration. "No toxic reactions have been found by clinical and laboratory observations, including a battery of seven tests of hepatic function and needle biopsies of the liver in 17 patients after one year of therapy."[1] However, patients must be told to expect pronounced warm flushing within approximately 15 minutes of the early doses. This effect is the normal initial response to high-dosage nicotinic acid, and is in no way harmful. It generally does not occur after one or two weeks.

VASTRAN FORTÉ contains anticholesterol dosage of nicotinic acid[1-13] *fortified by added B-complex factors to guard against vitamin deficiencies due to large dosage of a single B factor;*[14-15] *plus pyridoxine to improve utilization of unsaturated fatty acids in normal diets*[15-17] *and ascorbic acid*[18] *for support against degenerative arterial changes.*

Each VASTRAN FORTÉ Capsule contains: nicotinic acid, 375.0 mg.; ascorbic acid, 50.0 mg.; riboflavin, 2.5 mg.; thiamine mononitrate, 5.0 mg.; pyridoxine hydrochloride, 0.5 mg.; calcium pantothenate, 2.5 mg.; cobalamin concentrate (vitamin B_{12} activity), 10.0 mcg. **Dosage:** Initial Dosage—2 capsules four times a day after meals for twelve weeks. Thereafter dosage should be adjusted according to response. Maintenance requirements may vary from 1 capsule q.i.d. to 4 capsules q.i.d. **Supply:** Bottles of 100.

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Bibliography: 1. Parsons, W. B., Jr., and Flinn, J. H.: A.M.A. Arch. Int. Med. *103*:783, 1959. 2. Parsons, W. B., Jr., and Flinn, J. H.: J.A.M.A. *165*:234 (Sept. 21) 1957. 3. O'Reilly, P. O.: Canad. M. A. J. *78*:402 (March 15) 1958. 4. Altschul, R., and Hoffer, A.: Arch. Biochem. *73*:420, 1958. 5. Achor, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, R. F.: Circulation *17*:497, 1958 6. Altschul, R., and Hoffer, A.: Circulation *16*:499, 1957. 7. Hoffer, A., and Callbeck, M. J.: J. Ment. Sc. *103*:810, 1957. 8. Parsons, W. B., Jr., and Flinn, J. H.: Circulation *16*:499, 1957. 9. Achor, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, B. F.: Circulation *16*:499, 1957. 10. O'Reilly, P. O.; Demay, M., and Kotlowski, K.: Arch. Int. Med. *100*:797, 1957. 11. deSoldati, L.; Stritzler, G., and Balassanian, S.: Prensa méd. argent. *44*:3286 (Nov. 8) 1957. 12. Parsons, W. B., Jr., *et al.*: Proc. Staff Meet. Mayo Clin. *31*:377 (June 27) 1956. 13. Altschul, R; Hoffer, A., and Stephen, J. D.: Arch. Biochem. *54*:588, 1955. 14. Seebrell, W H., and Harris, R. S.: The Vitamins; Chemistry, Physiology, Pathology, New York, Academic Press, 1954, vol. 2, p. 551. 15. Gregory, I.: J. Ment. Sc. *101*:85, 1955. 16. Sinclair, H. M.: Lancet *1*:381, 1956. 17. Page, I. H., *et al.*: J.A.M.A. *164*:2048 (Aug. 31) 1957. 18. Rosenfeld, L.: Am. J. Clin. Nutrition *5*:286, 1957.

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Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

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Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
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- Establishes positive nitrogen balance
- Improves appetite, increases muscular weight
- Produces a sustained sense of well-being

Durabolin® *a new, potent, long-acting biologic stimulant,* exerts profoundly beneficial effects on both metabolic processes and emotional outlook. By increasing the utilization of dietary protein, DURABOLIN rapidly establishes a sustained positive nitrogen balance. Appetite improves dramatically. The resulting weight gain takes the form of solid, working, lean tissue—without edema. And the patient *feels* better. A weekly intramuscular injection of DURABOLIN rapidly produces a *sustained* sense of well-being even in severely debilitated patients, and this mood-brightening property makes DURABOLIN a valuable palliative, especially in metastatic, terminal mammary cancer.

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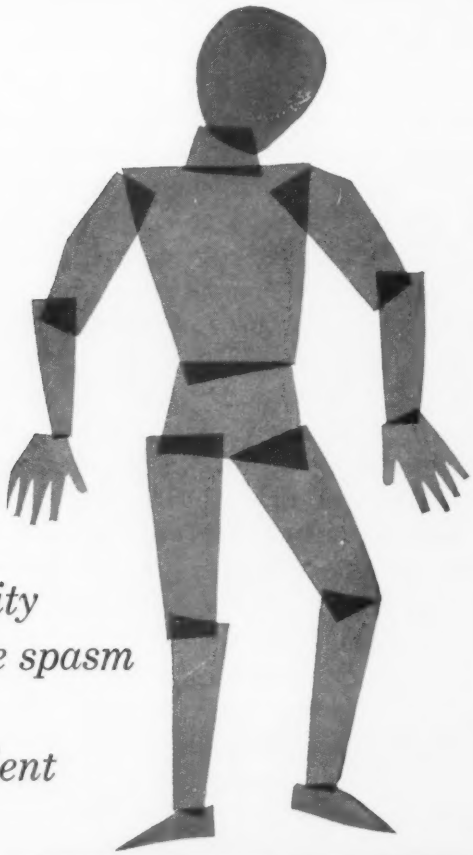

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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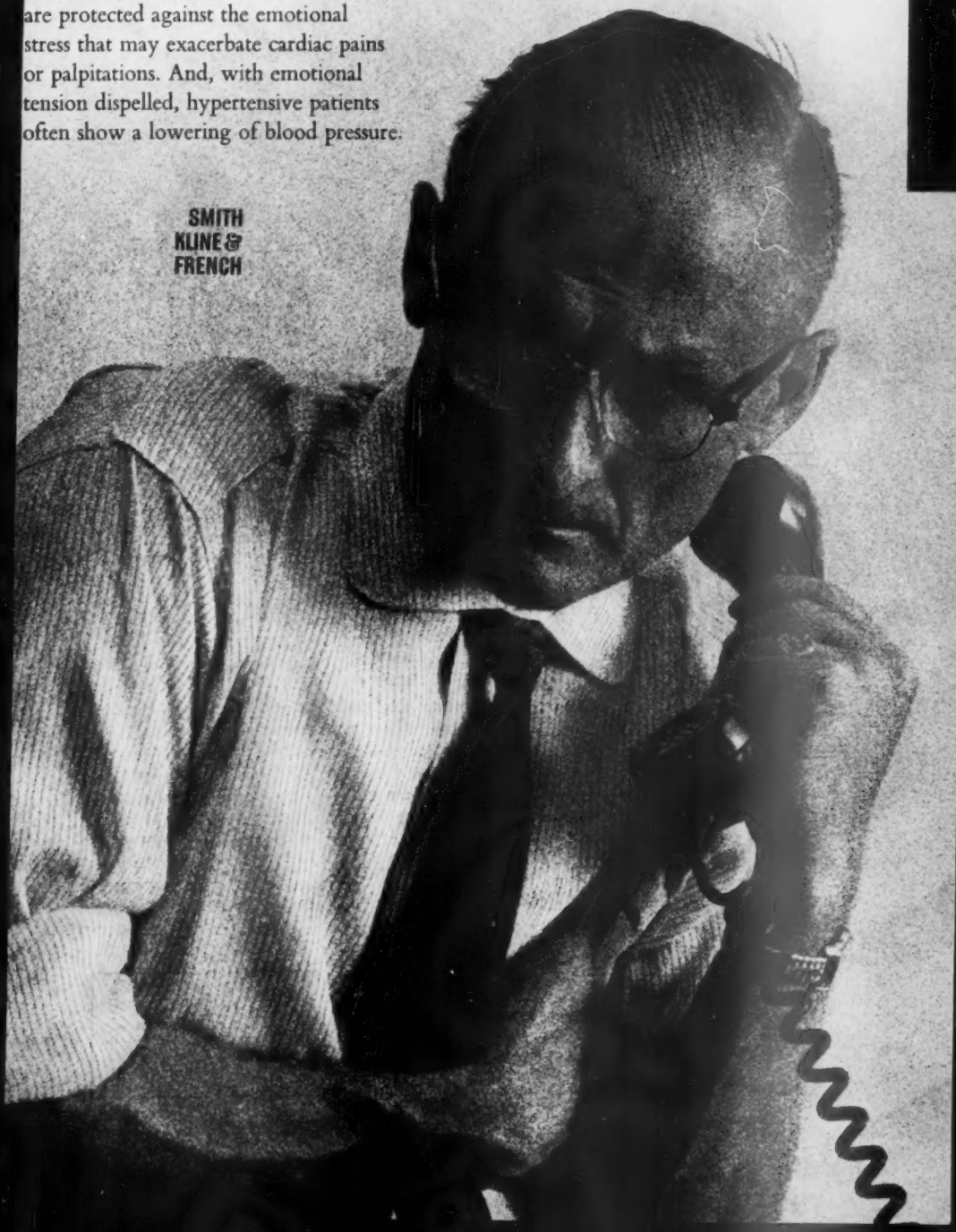

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of
unprecedented effectiveness
for
angina pectoris

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3 consistent effect
4 unusual safety

ISORDIL significantly reduces the number, duration, and severity of anginal attacks, often when other long-acting coronary vasodilators fail. Exercise tolerance is increased, pain decreased, and the requirements for nitroglycerin either drastically curtailed or eliminated.

ISORDIL acts rapidly in comparison with other prophylactic agents, and patients usually experience benefits within 15 to 30 minutes. The effects of a single dose of ISORDIL persist for 4 to 5 hours. Thus, for most patients, convenient q.i.d. administration is highly satisfactory.

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Markedly reduces number of anginal attacks:

Albert[5] found that of 29 patients receiving ISORDIL, 25 responded well, 1 moderately well, and 1 not at all. Effectiveness could not be judged in 2 patients. For those who responded well, the frequency of anginal attacks was quickly reduced from a daily average of 5 to 1.2. Continued use of ISORDIL further reduced the frequency of attacks.

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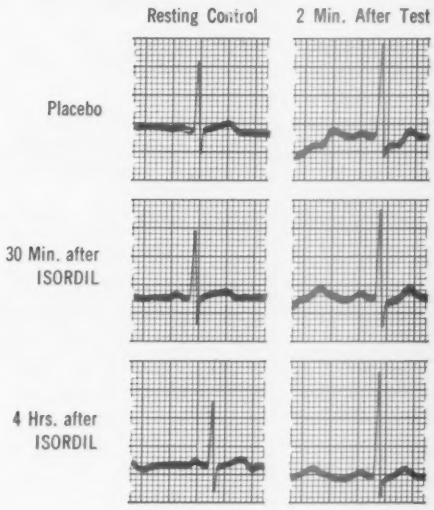
Rapid onset and prolonged action a function of solubility and metabolism:

Pharmacologic studies indicate that the rapid onset and prolonged action shown by ISORDIL are related to its high solubility and low rate of metabolism.[7] Incubation with liver slices suggest rapid absorption and delayed inactivation by the liver.

Master Test Responses (Lead V_4) in a 58-Year-Old Male with Angina Pectoris[6]



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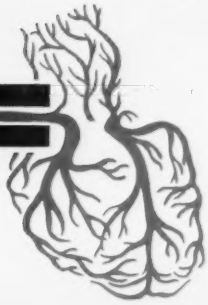

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- **Reduces number, duration, and severity of anginal attacks**

"Isordil is a new and effective agent for therapy of angina pectoris."—Russek[6]

Composition: Each white, scored tablet of ISORDIL (Isosorbide Dinitrate) contains 10 mg. of 1,4,3,6-dianhydro-sorbitol-2,5-dinitrate.

Action: Following oral administration of ISORDIL, the effects of coronary vasodilatation are apparent within 15 to 30 minutes and persist for 4 to 5 hours.

Indications: ISORDIL is indicated for the therapeutic and prophylactic management of angina pectoris and coronary insufficiency. It is often useful in patients only partially responsive to other long-acting coronary vasodilators.

Dosage: ISORDIL is administered orally. Average dose is one tablet (10 mg.) taken one half hour before meals and at bedtime. Individualization of dosage may be necessary for optimum therapeutic effect; dosage may vary from 5 mg. to 20 mg. q.i.d.

Side Effects: Side effects are few, infrequent, and mild. Transitory headache, common to effective nitrate or nitrite therapy, has occurred. This usually responds to administration of acetylsalicylic acid, and disappears with continued therapy. When headache is persistent, reduction in dosage may be required.

Caution: ISORDIL should be given with caution in patients with glaucoma.

Supplied: Bottles of 100.

References: 1. Riseman, J.E.F., et al.: Circulation **17**:22-39 (Jan.) 1958. 2. Sherber, D.A.: Personal Communication (Oct., 1959). 3. Case Reports on File, Ives-Cameron Company (1958-1959). 4. Summary of Case Reports on File, Ives-Cameron Company (1958-1959). 5. Albert, A.: Personal Communication (Oct., 1959). 6. Russek, H.I.: Personal Communication (Oct., 1959). 7. Harris, E., et al.: Personal Communication (Oct., 1959).

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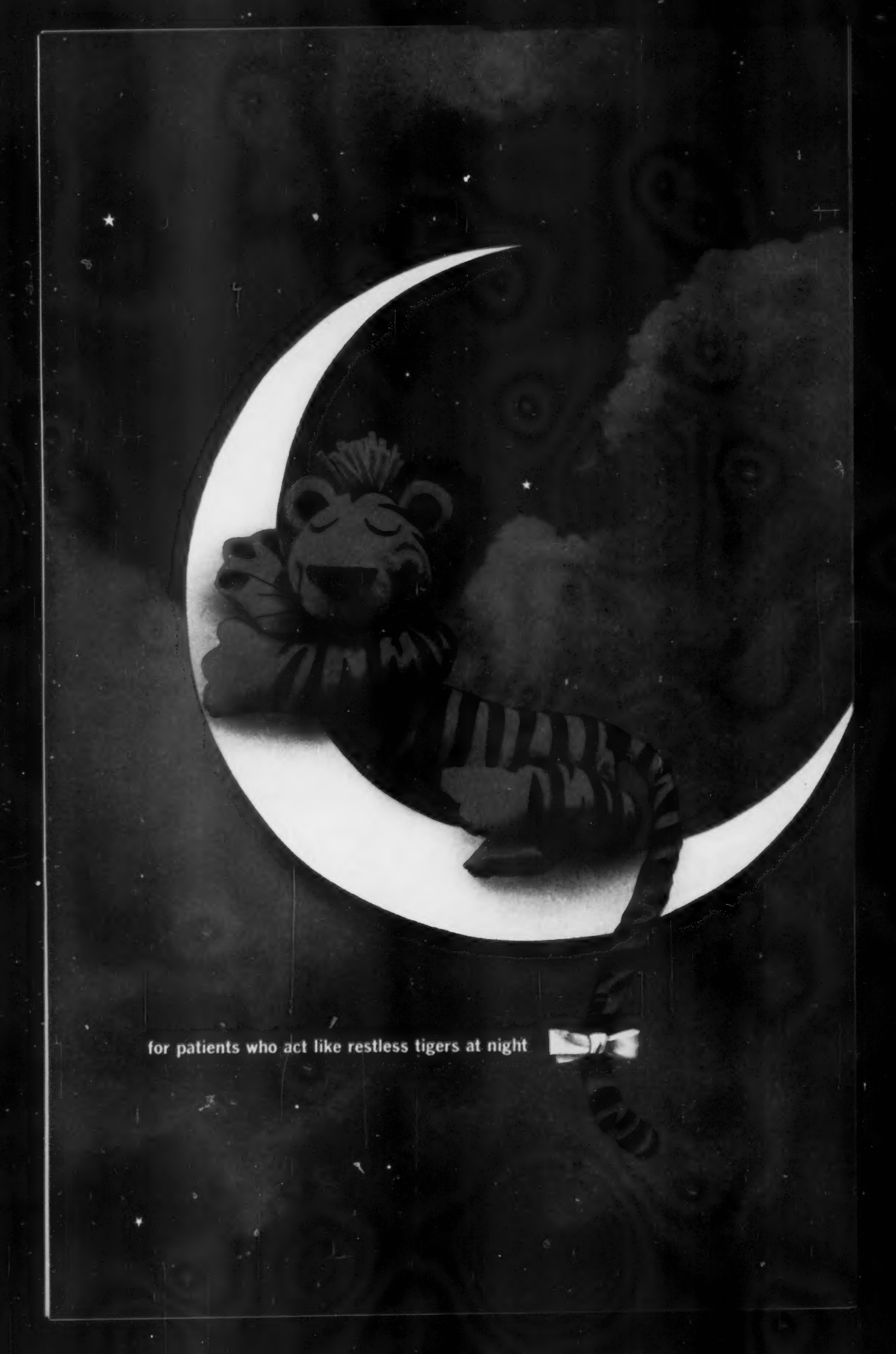
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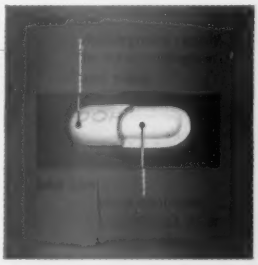
1. Schlesinger, E. B.: Tr. New York Acad. Sc. 2:6 (Nov.) 1948. **2.** Richards, R. K., and Taylor, J. D.: Anesthesiology 17:414, 1956. **3.** Shideman, F. E.: Postgrad. Med. 24:207, 1958. **4.** Berger, F.: Pharmacol. Rev. 1:243, 1949.



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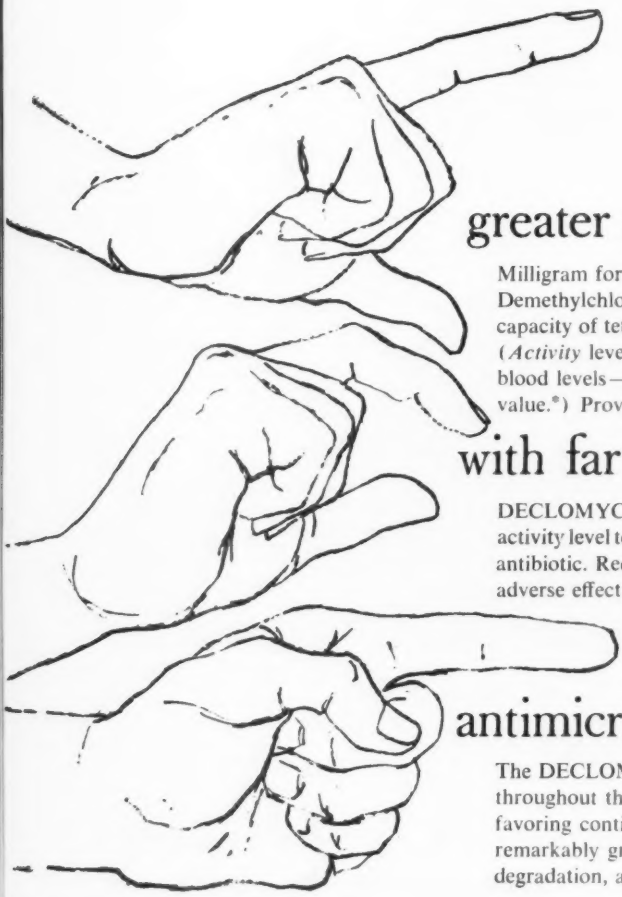

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*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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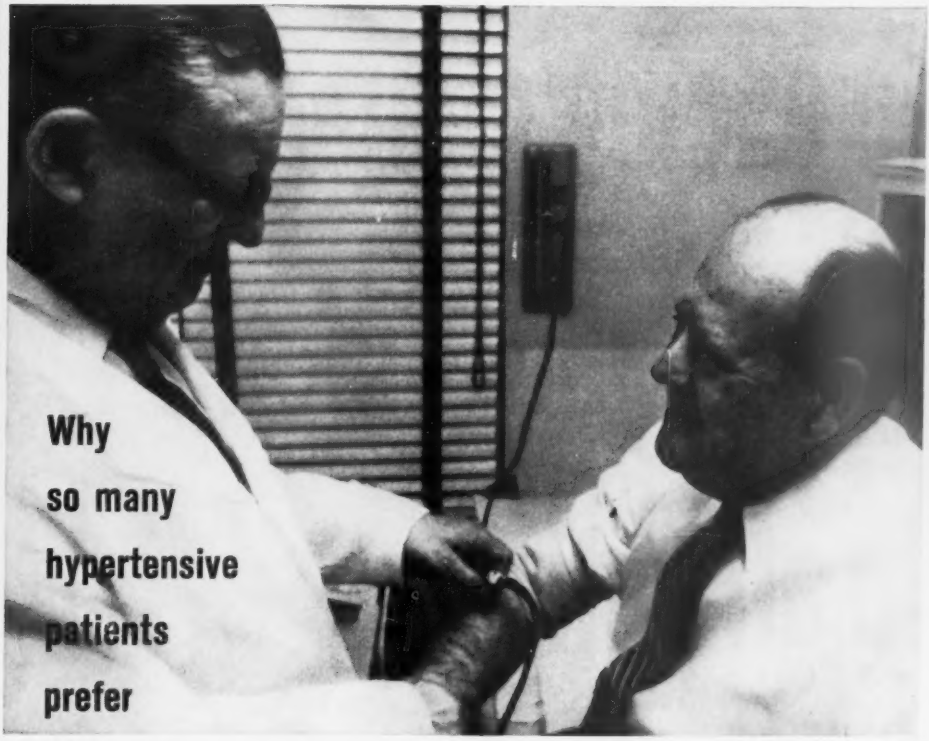

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*Herrmann, G. R., Vogelpohl, E. B., Hejtmancik, M. R., and Wright, J. C.: J.A.M.A. 169:1609 (April 4) 1959.

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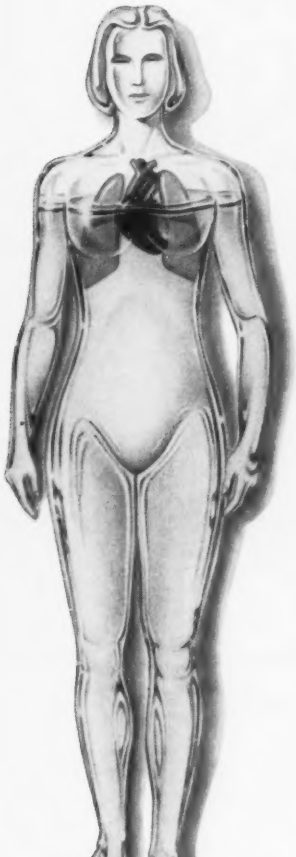

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Philadelphia 1, Pa.

Does more than curb appetite...
also relieves the tensions of dieting

Appetrol®

DEXTRO-AMPHETAMINE + MILTOWN®

Helps you keep your patient on your diet

AN EXTENSIVE SURVEY shows that in 68% of overweight persons there is an emotional basis for failure to limit food intake.[1] Appetrol has been formulated to help you overcome this problem and to keep your overweight patient on your diet.

THIS NEW ANORECTIC does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Miltown to relieve the tensions of dieting which undermine her will power.

IN PRESCRIBING APPETROL, you will find that your patient is relaxed and more easily managed so that she will stay on the diet you prescribe.

Usual dosage: 1 or 2 tablets one-half to 1 hour before meals.

Each tablet contains: 5 mg. dextro-amphetamine sulfate and 400 mg. Miltown (meprobamate, Wallace).

Available: Bottles of 50 pink, uncoated tablets.

1. Kotkov, B.. Group psychotherapy with the obese. Paper read before The Academy of Psychosomatic Medicine, October 1958.

WALLACE LABORATORIES, *New Brunswick, N. J.*

CPL-316

now...ulcer patients sleep through the night without pain or discomfort

new TRAL® 75 mg. Gradumet®

(Hexocyclium Methylsulfate in Long-Release Dose Form*, Abbott)

new anticholinergic dosage form aimed specifically at controlling nocturnal secretion

new ataractic-anticholinergic combination for medical management of functional bowel disease

new FILMTAB® TRALCYON™

(Hexocyclium Methylsulfate with Ectylurea, Abbott)

combining a highly selective anticholinergic with one of the most subtle and safe calmatives

New TRALCYON Filmtabs are indicated for the management of gastrointestinal dysfunction caused or aggravated by anxiety or tension. Disorders such as spastic and irritable colon, intestinal colic, hypermotility of the stomach or intestines and anxiety neuroses with vague gastrointestinal complaints respond well to treatment with Filmtab TRALCYON. When psychogenic factors aggravate an established organic lesion such as peptic ulcer, ulcerative colitis, or biliary tract disease, TRALCYON will usually produce superior benefit to the administration of an anticholinergic agent alone.

TRALCYON Filmtabs (List No. 6980), each containing TRAL®, 25 mg., with ectylurea, 300 mg., are available at all pharmacies, in bottles of 50 and 500.

ABBOTT

*Film-in-Film-Sealed Tablets, Abbott U. S. Pat. No. 2,851,085

whenever digitalis is needed

'LANOXIN'® brand DIGOXIN

formerly known as Digoxin 'B. W. & Co.'

"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

'LANOXIN' TABLETS
0.25 mg. scored (white)
0.5 mg. scored (green)

'LANOXIN' INJECTION
0.5 mg. in 2 cc. (I.M. or I.V.)

'LANOXIN' ELIXIR PEDIATRIC
0.05 mg. in 1 cc.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N.Y.

"... which antacid? Rorer's Maalox. Excellent results, no constipation plus a pleasant taste that patients like."

MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

TABLET MAALOX No. 2: 0.8 Gram, double strength (equivalent to two teaspoonfuls), Bottles of 50 and 250.

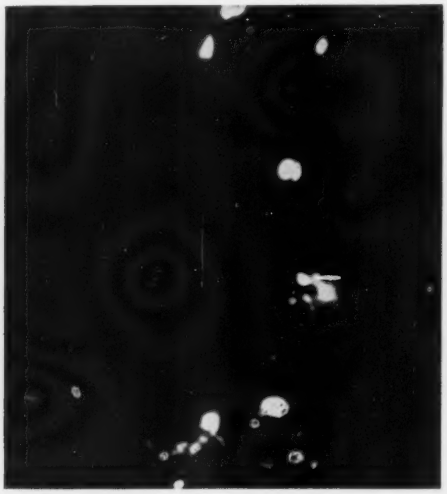
Samples on request.

WILLIAM H. RORER, INC., Philadelphia 44, Pennsylvania

Please Mention this Journal when writing to Advertisers

Clarin* can do this for your postcoronary patients

WITHOUT CLARIN, turbid blood serum five hours after a fat meal: This unretouched dark-field photomicrograph (2500X) shows potentially hazardous fat concentrations circulating in the blood stream of a patient after a standard fat meal.



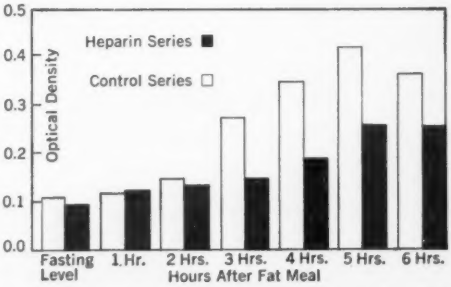
WITH CLARIN, clear blood serum five hours after a fat meal: After eating a standard fat meal as at left, the same patient has taken one sublingual Clarin tablet. Note marked clearing effect and reduction in massive fat concentrations in this unretouched photomicrograph (2500X).

CLARIN is sublingual heparin potassium. One mint-flavored tablet taken after each meal effectively "causes a marked clarification of postprandial lipemic serum."[1] Clarin facilitates the normal physiologic breakdown of fats, with no effects on the blood-clotting mechanism.[1] It therefore provides important benefits for your postcoronary patients.

Indication: For the management of hyperlipemia associated with atherosclerosis.

Dosage: After each meal, hold one tablet under the tongue until dissolved.

Supplied: In bottles of 50 pink, sublingual tablets, each containing 1500 I.U. heparin potassium.



Average serum optical density in 36 patients after fat meal with and without sublingual heparin.[2]

*Registered trade mark. Patent applied for.

1. Fuller, H. L.: Angiology 9:311 (Oct.) 1958.
2. Shaftel, H. E., and Selman, D.: Angiology *10*:131 (June) 1959.

Thos. Leeming & Co., Inc. New York 17, N. Y.

DEXAMYL® SPANSULE®

brand of dextro amphetamine and amobarbital — brand of sustained release capsules

to improve mood and restore drive in the nervous, depressed patient

Caldwell and Nowers[1] state: "The particularly desirable results achieved in depressed, tense, 'nervous' women suggest that, for some patients, ['Dexamyl'] may be more appropriate than the widely used tranquilizers which create an attitude of indifferent calm." These investigators add that 'Dexamyl' "seems to enhance initiative at the same time that it lessens tension, thereby producing a mental attitude which enables the patient to face up to and act upon her problems."

Patients find the 'Spansule' capsule form especially convenient, because they needn't carry medication with them during the day. 'Spansule' capsules also assure fewer forgotten doses, since only one capsule taken in the morning gives 10- to 12-hour therapeutic effect.

'Dexamyl' *Spansule* capsules are available in two strengths, No. 2 (standard strength) and No. 1 (lower strength).

1. Caldwell, W.G., and Nowers, W.: California Med. *88*:380 (May) 1958.

leaders in psychopharmaceutical research

SMITH KLINE & FRENCH

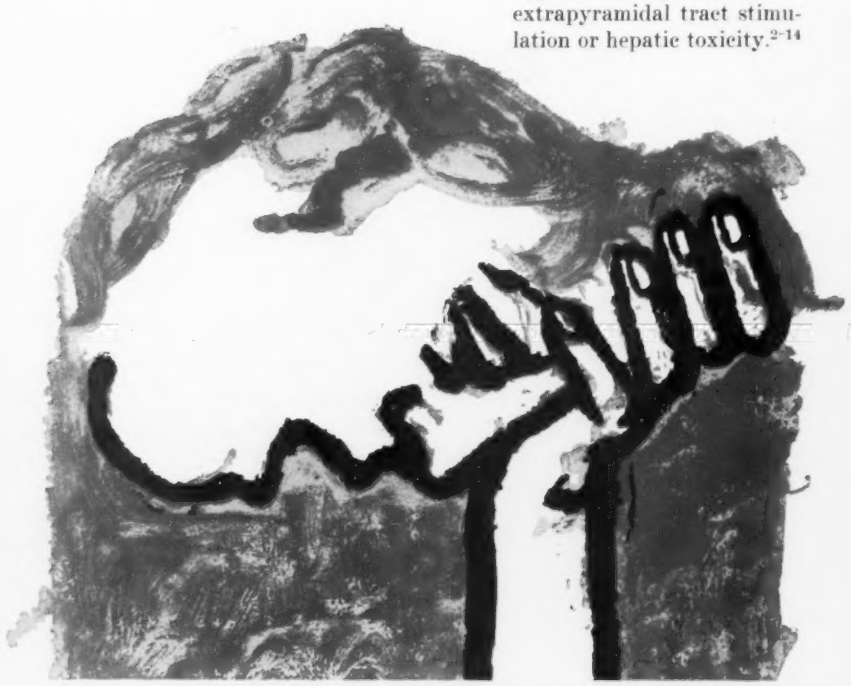
stop as well as prevent nausea and vomiting

Tigan

now in oral, parenteral, and suppository forms

effective but not "side effective"

Tigan blocks emetic impulses at the chemoreceptor trigger zone (CTZ),[1] a medullary structure activating the vomiting center. While Tigan shares with the phenothiazines the mode of antiemetic action, this is their only similarity.[1] In extensive clinical studies[2-14] Tigan, unsurpassed in specificity, has exhibited a virtually complete absence of side effects. Tigan has demonstrated no sedative or tranquilizing properties, no hypotensive or supramedullary effects, no extrapyramidal tract stimulation or hepatic toxicity.[2-14]



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no special precautions—
no known contraindications

in nausea/vomiting of gastrointestinal disorders — Complete or moderate relief in 78 per cent of acute or chronic gastroenteritis patients;[13] "We did not find a single toxic reaction . . . no side effects, such as sedation, skin rash . . . no changes in pulse, respiration, or . . . blood pressure."[13]

in nausea/vomiting of pregnancy — No evidence of sedation or other side effects[12] observed in a series of patients of whom 94 per cent became asymptomatic on Tigan. On other antiemetic medication, several had failed to respond or had complained of drowsiness.[12]

in nausea/vomiting of radiation sickness — Protected with Tigan "... not one patient had to discontinue [deep radiation] treatments. . . ."[5]

in nausea/vomiting of drug administration — "... large intermittent dose[s] of [nitrogen mustard and other drug] therapy could be given without the associated nausea and vomiting that we had seen before."[7]

Tigan

specific antiemetic antinauseant

no sedative properties
no tranquilizer side effects

Suggested uses: Both prophylactic and therapeutic control of nausea and vomiting associated with pregnancy, travel sickness, gastrointestinal disorders, operative procedures, carcinomatoses, toxicoses, other underlying disease processes, drug administration and radiation therapy.

Dosage: Adults — 1 or 2 capsules, orally, 2 cc intramuscularly, q.i.d. or 1 suppository, q.i.d. For children's dosage, consult literature.

In nausea and vomiting of pregnancy — Satisfactory control is usually achieved with an initial dose of two capsules immediately upon awakening. If possible, the patient should remain in bed for one-half to one hour following this dose. When nausea and vomiting are not confined to the morning hours, supplemental doses of one or two capsules should be given throughout the day at intervals of three to four hours.

How Supplied: **Tigan** capsules, 100 mg, blue and white — bottles of 100 and 500. Tigan ampuls, 2 cc (100 mg/cc)— boxes of 6 and 25. Tigan Pediatric Suppositories, 200 mg, boxes of 6.

TIGAN® Hydrochloride—
4-(2-dimethylaminoethoxy)-
N-(3,4,5-trimethoxybenzoyl)
benzylamine hydrochloride
ROCHE®

ROCHE
LABORATORIES
Division of
Hoffmann-La Roche Inc.
Nutley 10, N. J.

References: **1.** W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap., 126*:270, 1959. **2.** W. B. Abrams, I. Roseff, J. Kaufman, L. Goldman and A. Bernstein, to be published. **3.** I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp., 9*:189, 1958. **4.** O. C. Brandman, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **5.** J. A. Lucinian, *ibid.* **6.** D. W. Molander, *ibid.* **7.** B. I. Shnider, *ibid.* **8.** W. S. Derrick, *ibid.* **9.** B. Wolfson and F. F. Foldes, *ibid.* **10.** L. McLaughlin, *ibid.* **11.** Reports on file, Roche Laboratories. **12.** Personal communications. **13.** W. K. Gauthier, Discussant at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. **14.** H. E. Davis, *ibid.*

AN AMES CLINIQUICK®

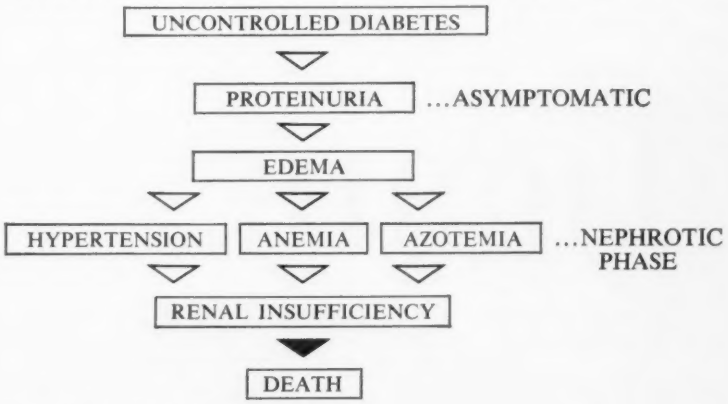
CLINICAL BRIEFS FOR MODERN PRACTICE

Why is the diabetic especially vulnerable to nephropathy?

Because the kidney is the body organ most susceptible to alteration in structure and function by the diabetic state. Seventy-five per cent of all deaths due to diabetes result from cardiovascular-renal complications. Of this group, one-fifth of the complications are primarily renal in origin.

Source: Whitehouse, F. W.: Postgrad. Med. *24*:54, 1958.

NATURAL HISTORY OF DIABETIC NEPHROPATHY



Adapted from Whitehouse, F. W.: *op. cit.*

CHECK THE DIABETIC FOR GLYCOSURIA... **AND PROTEINURIA**
PROBABLY THE BEST SINGLE INDICATOR OF RENAL DISORDER

URISTIX®

BRAND *Reagent Strips*

colorimetric "dip-and-read" combination test for *protein* and *glucose* in urine

1 DIP... 10 SECONDS... 2 RESULTS

AMES COMPANY, INC
Elkhart • Indiana
Toronto • Canada

- unaffected by turbidity, drug metabolites or other urine constituents
- standardized color charts provide reference points for rapid reading

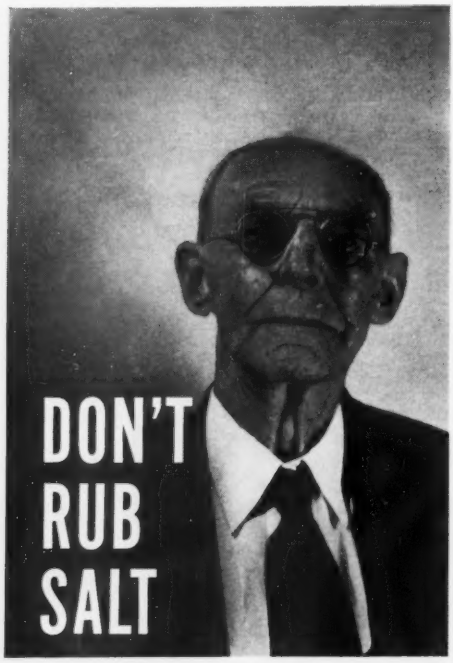
URISTIX® Reagent Strips – Bottles of 125. 83760

for laxative results without laxative harshness

in chronic constipation **DOXIDAN** THE SURFACTANT LAXATIVE

Provides positive easy evacuation of a soft, formed, "normal" stool through the synergistic action of the gentle peristaltic stimulant, Danthron, with the superior surfactant, calcium bis-(dioctyl sulfosuccinate). No "griping" or cramping—no bloating—no oily leakage or interference with vitamin absorption.

DOSAGE: For adults and children over 12, one or two capsules. For children, age 6 to 12, one capsule. Administered at bedtime for 2 or 3 days or until bowel movements are normal. Supplied in bottles of 30 and 100 soft gelatin capsules.



IN HIS CARDIAC WOUND

Modern saluretics may *seem* to have made unlimited salt intake possible for cardiac and hypertensive patients. Yet despite the improvements in diuretic therapy, sodium restriction is still important in the prophylaxis of edema. The wise physician does not add needlessly to the burden of his patient, nor test unnecessarily the power of the drugs he prescribes. It makes good sense to him to prescribe DIASAL—which looks, tastes and flavors food exactly like salt . . . but is sodium free.

Diasal contains potassium chloride, glutamic acid and inert ingredients. Supplied in shakers and 8 oz. bottles.

prescribe **DIASAL**®
sodium-free salt substitute

FOUGERA

E. Fougera & Co., Inc. • Hicksville, New York

Ann Woodward
Director

OF COURSE YOU CAN'T "TAKE IT EASY"

BUT you *can* extend the benefits of your skill and experience without extending yourself beyond reasonable limits. Many other busy physicians and surgeons have demonstrated the success of the plan which you, also, may desire to adopt: delegate some of your responsibilities to an associate whom you have (1) carefully selected; (2) proved competent by thorough induction into your methods.

The Woodward Bureau gives swift, systematic service in helping physicians and surgeons to find associates who measure up. Many fine men in all fields of medicine have sought such associate positions *and been located through our channels.*

Whether your requirements are on a permanent or temporary basis, we are prepared to assist you in finding an associate.

OUR 63RD YEAR

WOODWARD
MEDICAL PERSONNEL BUREAU
FORMERLY AZNOES • 185 N. WABASH • CHICAGO

Founders of the counseling service to the medical profession serving medicine with distinction over half a century

LIFE STORY

The leading site of cancer today is the colon and rectum. In 1958, 58,000 new cases were diagnosed.

The present 5-year survival rate for these cancers is less than 30%. This figure could be greatly increased by closing the very wide gap between *actual* and *possible* survival rates.

Earlier diagnosis is an immediate requirement. The American Cancer Society urges annual health checkups for all adults, and employment of digital and proctoscopic examinations of the rectum and colon by physicians, to find cancer in an early stage.

AMERICAN CANCER SOCIETY

a refinement in rauwolfia alkaloid therapy

moderil®

brand of rescinnamine

for better management of hypertension

a purified alkaloid of rauwolfia . . . lessens the frequency and/or severity of these reserpine side effects:

mental depression • bradycardia • sedation • weakness • fatigue • lassitude • sleepiness • nightmares • gastrointestinal effects

useful *alone* for gradual, sustained lowering of blood pressure in mild to moderate labile hypertension

useful *as an adjunct* to other antihypertensive agents, permitting their use in lower, better tolerated dosage

Professional information available on request

PFIZER LABORATORIES Division, Chas. Pfizer & Co. Inc., Brooklyn 6 N.Y. Pfizer *Science for the world's well-being™*

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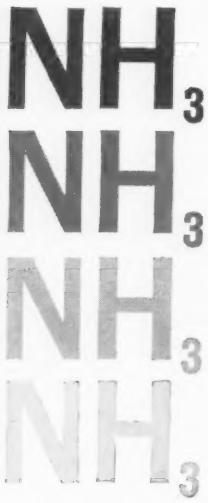


rational and
effective therapy
in **ammonia intoxication**

R-gene®

lowers blood ammonia

R-gene can prevent impending hepatic coma or shorten the duration of hepatic coma by detoxifying circulating ammonia, thus reducing elevated blood ammonia levels. R-gene, a solution of L-arginine, accelerates the conversion in the liver of toxic ammonia to nontoxic urea.

dramatically increases survival rate

In patients with hepatic coma a mortality rate of approximately 90 per cent is usual. Yet when R-gene was used as part of the therapeutic regimen, a rate of 30 per cent was reported in a group of patients half of whom were in deep coma.*

indicated as part of the regimen in any disease state where blood ammonia is elevated to toxic levels, as in: hepatic coma or impending hepatic coma; ammonia intoxication due to ingestion of ammonium salts; acute hepatic insufficiency; following massive gastrointestinal hemorrhage.

supplied in packages containing 400 cc. of a 5% solution of L-arginine in a 500 cc. Saftiflask®; 100 cc. Ambot® of 50% dextrose (to improve liver metabolism); and complete administration set with needles.

*Najarian, J. S., *et al.*: Am. J. Surg. 96:172, 1958.

SINCE CUTTER 1897 **CUTTER LABORATORIES** · Berkeley, California

Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—rapidly bactericidal against most intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE® (succinylsulfathiazole)—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help reduce intestinal hypermotility, help provide rapid symptomatic relief.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.

DBI

trademark, brand of Phenformin HCl

the "full-range" oral hypoglycemic agent
...safely lowers blood sugar in mild, moderate
and severe diabetes, in children and adults

start
low

The **"Start Low! Go Slow!"** dosage pattern with DBI enables a maximum number of diabetics to enjoy the convenience, comfort and satisfactory regulation of oral therapy in:

stable adult diabetes
unstable (brittle) diabetes
juvenile diabetes
sulfonylurea resistant diabetes

"Start Low! Go Slow" means low initial dosage (25 mg., or 50 mg. in divided doses, per day) with small dosage increments (25 mg.) every 3rd or 4th day until blood sugar levels are adequately controlled. Injected insulin is reduced gradually with each increase in DBI dosage. Satisfactory regulation of mild stable diabetes is usually achieved with DBI alone.*

On **"Start Low! Go Slow!"** dosage, DBI is relatively well tolerated.

Over 3000 diabetics have been carefully studied on DBI daily for varying periods up to three years. No histologic or functional changes in liver, blood, kidneys, heart or other organs were seen.

DBI (N^1-β-phenethylbiguanide) is available as white, scored tablets of 25 mg. each, bottles of 100.

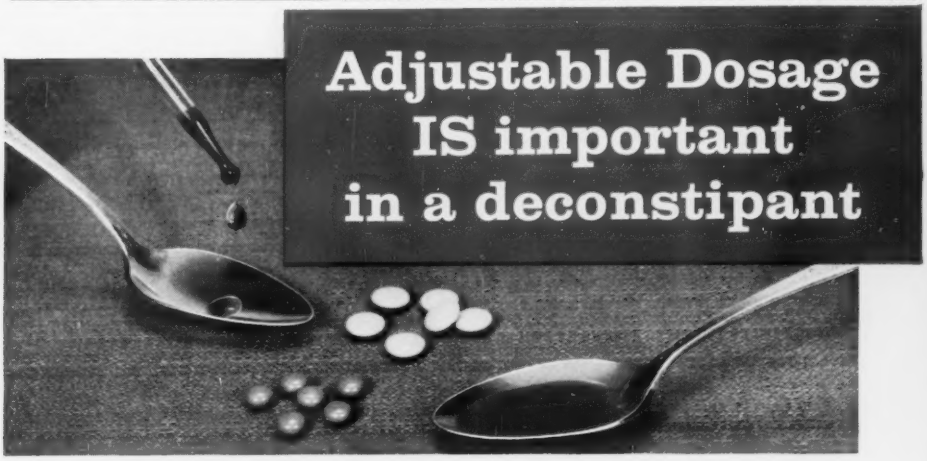
*Send for brochure with complete dosage instructions for each class of diabetes, and other pertinent information.

go slow

an original development from the research laboratories of

u. s. vitamin & pharmaceutical corporation

Arlington-Funk Laboratories, division
250 East 43rd Street, New York 17, N.Y.



that's why MODANE offers you a dosage form for every patient

TABLETS REGULAR (yellow) *For your average adult patient.*

Each tablet contains 75 mg. danthron, 25 mg. calcium pantothenate. Dose — 1 tablet immediately after the evening meal.

TABLETS MILD (pink) *for hypersensitives and children (6 to 12 yrs).*

Each tablet contains 37.5 mg. danthron, 12.5 mg. calcium pantothenate. Dose — 1 tablet to be taken immediately after the evening meal.

LIQUID *... for geriatric, pediatric, and "liquid only" patients.*

Each teaspoonful contains 37.5 mg. danthron and 12.5 mg. calcium pantothenate. Dose — 1 teaspoonful or fraction thereof, according to age and condition, immediately after the evening meal.

MODANE'S danthron (1, 8-dihydroxyanthraquinone) in individualized dosages assures safe, gentle overnight relief — without irritation or griping — acts systemically on the large intestine.

MODANE'S calcium pantothenate offers neurohumoral aid to rehabilitation of the bowel which, from distention and overwork, has become flaccid and atonic.

THE WARREN-TEED PRODUCTS COMPANY
COLUMBUS 8, OHIO

Dallas Chattanooga Los Angeles Portland

FROM MARKED IMPROVEMENT
to COMPLETE CONTROL
of GRAND MAL SEIZURES
with

"MYSOLINE"®

wide margin of safety

CLINICAL EVALUATION OF 486
EPILEPTIC PATIENTS* SHOWED THAT:

In patients who had received no previous anticonvulsant medication,
"Mysoline" therapy alone provided marked improvement to complete control of major motor attacks in the majority of patients.

In patients only partially controlled with maximum dosages of other anticonvulsants,
the addition of "Mysoline" therapy was followed by marked improvement to complete control of grand mal attacks in 39% of the patients.

In patients refractory to maximum dosages of other anticonvulsants,
"Mysoline" employed alone provided marked improvement to complete control of major motor attacks in 34% of the patients.

In 39 patients with mixed seizures,
"Mysoline" provided improvement to marked control in 49% of the patients.

The dramatic results obtained with "Mysoline" advocate its use as first choice of effective and safe therapy in the control of grand mal and psychomotor attacks.

Supplied: 0.25 Gm. scored tablets, bottles of 100 and 1,000.

Literature on request.

*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

5933

Ayerst

AYERST LABORATORIES

New York 16, N. Y. Montreal, Canada

"Mysoline" is available in the United States by arrangement with Imperial Chemical Industries, Ltd.

NEW

DEPINAR

Truly repository injectable B12 quickly achieves and sustains high B12 blood levels for a minimum of 28 days

The Depinar special repository base permits slow absorption from the injection site, thus decreasing the need for frequent administration. Depinar continually bathes the tissues in vitamin B_{12} to provide more effective therapy and make patients feel better longer. A recent clinical report* shows over 98% of Depinar is retained after one week . . . and "Serum level vitamin B_{12} . . . sustained for 28 days or more from the single dose."

Each package of Depinar consists of a multiple dose vial, containing cyanocobalamin zinc tannate (lyophilized) equivalent to 2500 mcg. vitamin B_{12}. The vial of diluent contains 5 cc. Sodium Chloride Solution for Injection. When reconstituted, each ml. of Depinar contains 500 mcg. vitamin B_{12}.

*Thompson, R. E., and Hecht, R. A.: Am. J. Clin. Nutrition 7:311-317 (May-June) 1959.

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ARMOUR

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THE AMERICAN COLLEGE OF PHYSICIANS

Schedule of Postgraduate Courses, Spring, 1960

The following courses have been arranged through the generous cooperation of the directors and the institutions at which the courses will be given. Customary tuition fees will be: members, $60.00; non-members, $80.00. Full details of these courses may be obtained through the Executive Offices of the College, 4200 Pine St., Philadelphia 4, Pa.

	March		April				May					June			
	21-25	28-April 1	4-8	11-15	18-22	25-29	2-6	9-13	16-20	23-27	May 30-June 3	6-10	13-17	20-24
Course No. 1, RECENT ADVANCES IN PHARMACOTHERAPY: University of Washington School of Medicine, Seattle, Wash.; Robert H. Williams, M.D., F.A.C.P., Director.	X		A.C.P. Annual Session, San Francisco										A.M.A. Meeting, Miami, Fla.	
Course No. 2, CURRENT CONCEPTS IN CLINICAL GASTROENTEROLOGY: Tulane and Louisiana State Universities Schools of Medicine, New Orleans, La.; G. Gordon McHardy, M.D., F.A.C.P., Director; Robert L. Simmons, M.D., and Helen Von Fossen, M.D., Associate Directors.		28-31												
Course No. 3, DERMATOLOGY FOR THE INTERNIST: University of Michigan Medical School, Ann Arbor, Mich.; Arthur C. Curtis, M.D., F.A.C.P., Director; E. Richard Harrell, M.D., Co-Director.						X								
Course No. 4, THE EARLY DETECTION AND PREVENTION OF DISEASES: University of Pennsylvania School of Medicine, Department of Public Health and Preventive Medicine, Philadelphia, Pa.; John P. Hubbard, M.D., F.A.C.P., and Norbert J. Roberts, M.D., F.A.C.P., Co-Directors.								X						
Course No. 5, CURRENT RESEARCH IN CARDIOVASCULAR DISEASES: National Heart Institute, Bethesda, Md.; Luther L. Terry, M.D., F.A.C.P., Director.									X					
Course No. 6, THE HYPERTENSIVE DISEASES: DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN ESSENTIAL, ADRENAL AND RENAL HYPERTENSION: Boston University, School of Medicine, Massachusetts Memorial Hospitals, Boston, Mass.; Robert W. Wilkins, M.D., F.A.C.P., Director.										X				
Course No. 7, INTERNAL MEDICINE: University of Indiana School of Medicine, Indianapolis, Ind.; John B. Hickam, M.D., F.A.C.P., Director.														X

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Bed of Digitalis purpurea
with Campanula (Canterbury Bells) in foreground

Not far from here are manufactured
from the powdered leaf
Pil. Digitalis (Davies, Rose)
0.1 Gram (1½ grains) or 1 U.S.P. Digitalis Unit.
They are physiologically standardized,
with an expiration date on each package.
Being Digitalis in its completeness,
this preparation comprises the
entire therapeutic value of the drug.
It provides the physician with a safe and effective
means of digitalizing the cardiac patient
and of maintaining the necessary saturation.
Security lies in prescribing the
"original bottle of 35 pills, Davies, Rose."

Clinical samples and literature sent to physicians on request

Davies, Rose & Co., Ltd. Boston 18, Mass.

Now

in inflammatory anorectal disorders . . .

The Promise of Greater Relief

the first suppository to contain

hydrocortisone for effective control of proctitis

- Proctitis accompanying ulcerative colitis
- Radiation proctitis
- Postoperative scar tissue with inflammatory reaction
- Acute and chronic nonspecific proctitis
- Acute internal hemorrhoids
- Medication proctitis
- Cryptitis

Ulcerative Colitis

Radiation Proctitis

Postoperative Scar Tissue

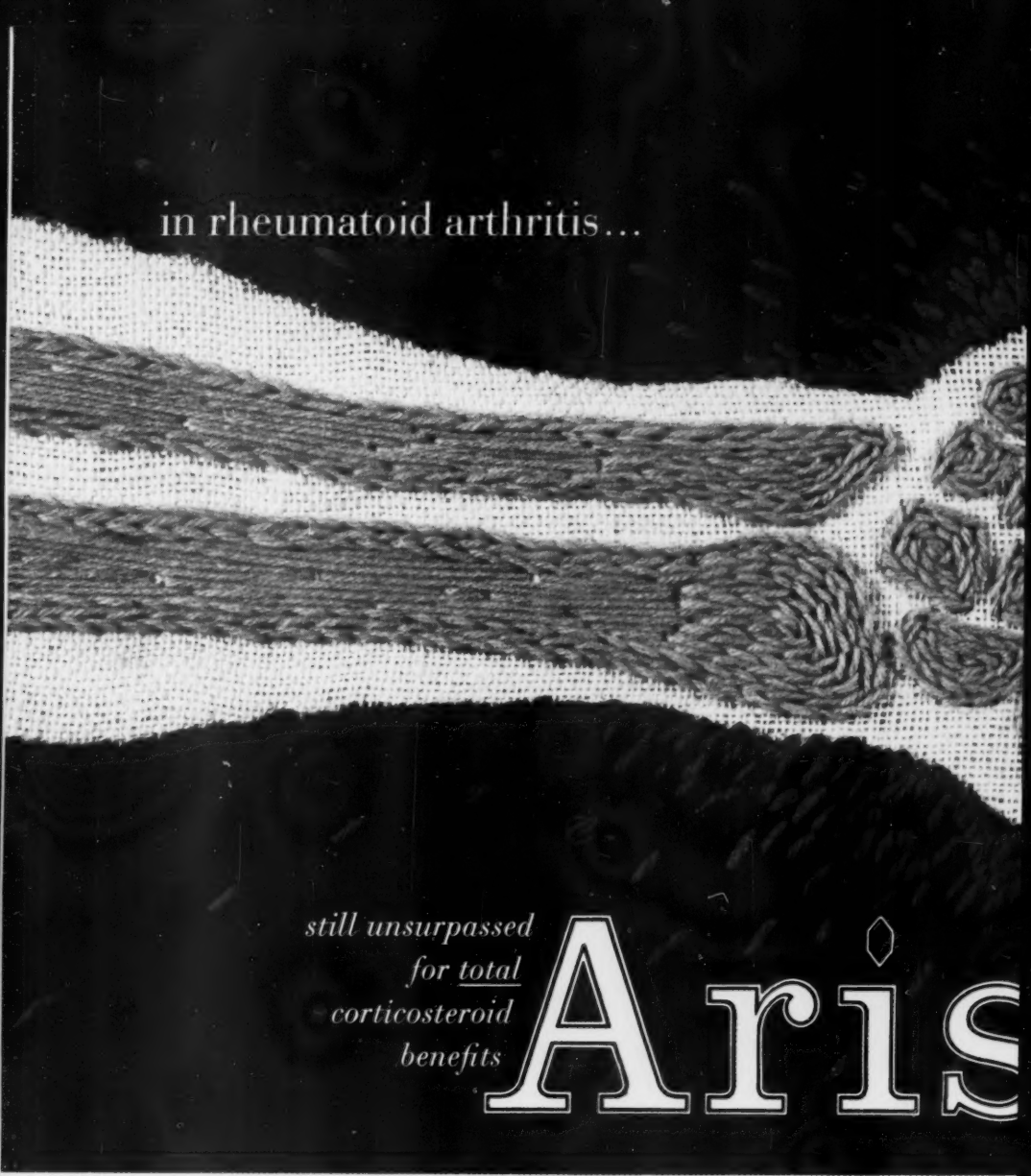
Supplied: Suppositories, boxes of 12. Each suppository contains 10 mg. hydrocortisone acetate, 15 mg. extract belladonna (0.19 mg. equiv. total alkaloids), 3 mg. ephedrine sulfate, zinc oxide, boric acid, bismuth oxyiodide, bismuth subcarbonate, and balsam peru in an oleaginous base.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth

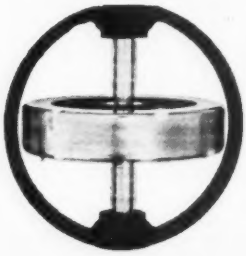
Wyeth

Philadelphia 1, Pa.

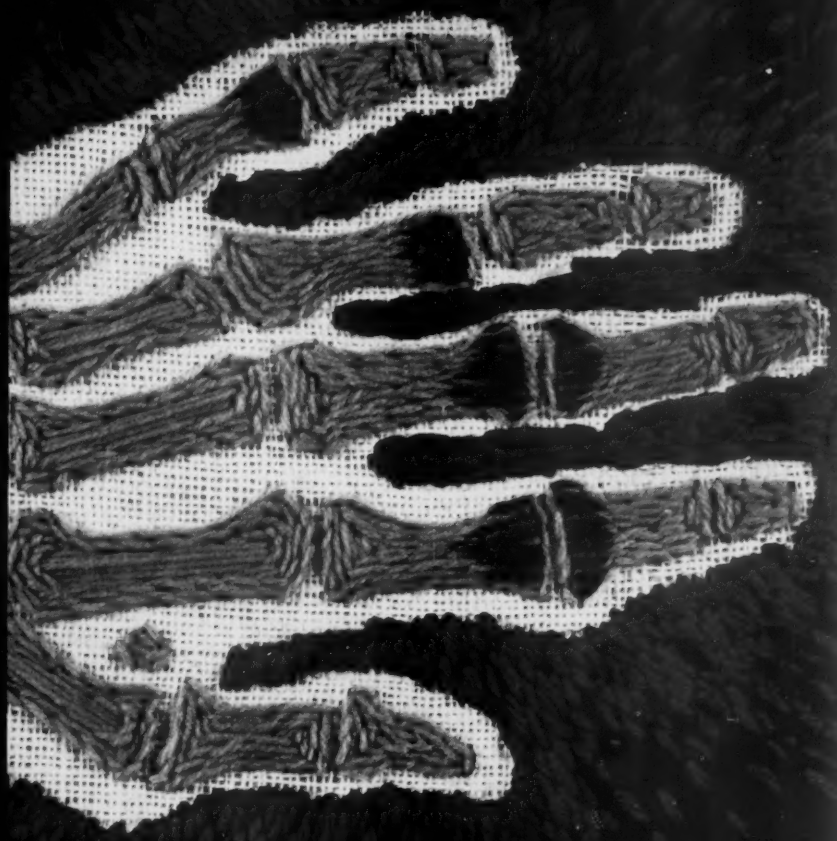


Substantiated by published reports of leading clinicians:

- **effective control** of inflammatory and allergic symptoms[1-9]



- **minimal disturbance** of the patient's **chemical** and psychic balance[2-17]



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A STATISTICAL REVIEW* OF THREE HUNDRED THIRTY-THREE CASES

**Records of Medical Department, Abbott Laboratories, North Chicago, Illinois*

SPONTIN (Ristocetin, Abbott) is a new antibiotic discovered and developed at Abbott Laboratories. Its two components, and B, have been isola line state from the fer of a new species of *Nocardia lurida*. Bot are active against gra teria and mycobacter mycete was isolated f ple collected from th Gods, Colorado Sp No other culture wh same antibiotic has

The chemical cha ristocetins are not c though they are kn teric substances con phenolic groups a ristocetin A and ris molecules with m the vicinity of 4000 have good stability pH range of bloo SPONTIN is a ly tion, derived fr material, represe ristocetins A an

Antimicrobial tion against gra ganisms, SPON effective than able antibiotics

Against pne cocci (except s cocci) the anti tericidal at th concentration hibits the gro also kills the

This obse for the majo lococci. Ho staphylococ have been t centration minimum i produce a this reaso SPONTIN for the trea and enterococcal infections.

Cultures of staphylococcus aureus, which are resistant to other antibiotics have been shown to be sensitive to SPONTIN. There has been no case reported in which a staphylococcal or enterococcal strain has exhibited a

SPONTIN

pH range of blood and SPONTIN is a lyophilized preparation, derived from pure crystalline material, representing a mixture of ristocetins A and B.

Antimicrobial Properties. In its action against gram-positive coccal or- SPONTIN is notably more

tly avail-

d strepto- of entero- riably bac- sage. The which in- organisms

holds true s of staphy- e strains of cocci which quired a con- her than the centration to ffect. It is for her dosage of recommended taphylococcal tions.

coccus aureus, o other antibi- to be sensitive s been no case aphylococcal or has exhibited a SPONTIN.

that the antibi- TIN is enhanced gamma globulin. supported by the *vivo* activity of mes greater than from the *in vitro*

estigators* have re- cal response follow- ration of SPONTIN dies have shown a vity on the part of ganism. Satisfactory may be expected sm requires up to 25 ONTIN for inhibition llowing table shows nsitivities of different he major pathogenic groups.

Summary and Conclusions

Major use has been treating staphylococcic infections. Of the total 333 cases, approximately one-third was treated for pneumonia; of these over 80% were either cured or improved. About 70% of these pneumonias were caused by staphylococci.

The next largest group included 46 patients with subacute bacterial endocarditis. About 50% of these infections were identified as staphylococcic and a further 15% as enterococcic. Other infections included 38 cases of septicemia, 32 abscesses and 24 patients with osteomyelitis.

The administration of SPONTIN brought about a cure in 60% of all the cases reviewed and improvement in a further 17%.

Side-effects were seldom troublesome when a daily dose of 2 Gm. was not exceeded. The incidence rose as the dosage was increased. The most disturbing side-effect after administration of SPONTIN has been neutropenia. However, in all instances this has responded to either discontinuance of medication or reduction in dose.

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from Schering
for seasonal asthma
and allergic dermatoses

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What are its advantages?

What's its dosage?

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POLANIL

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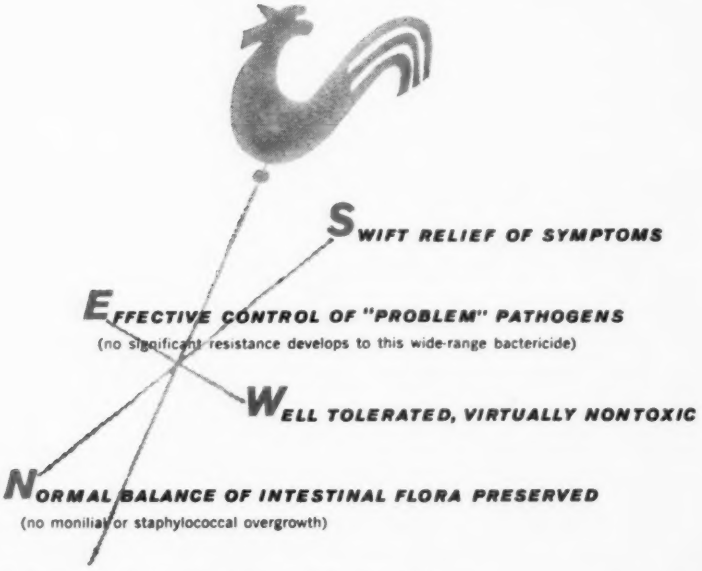
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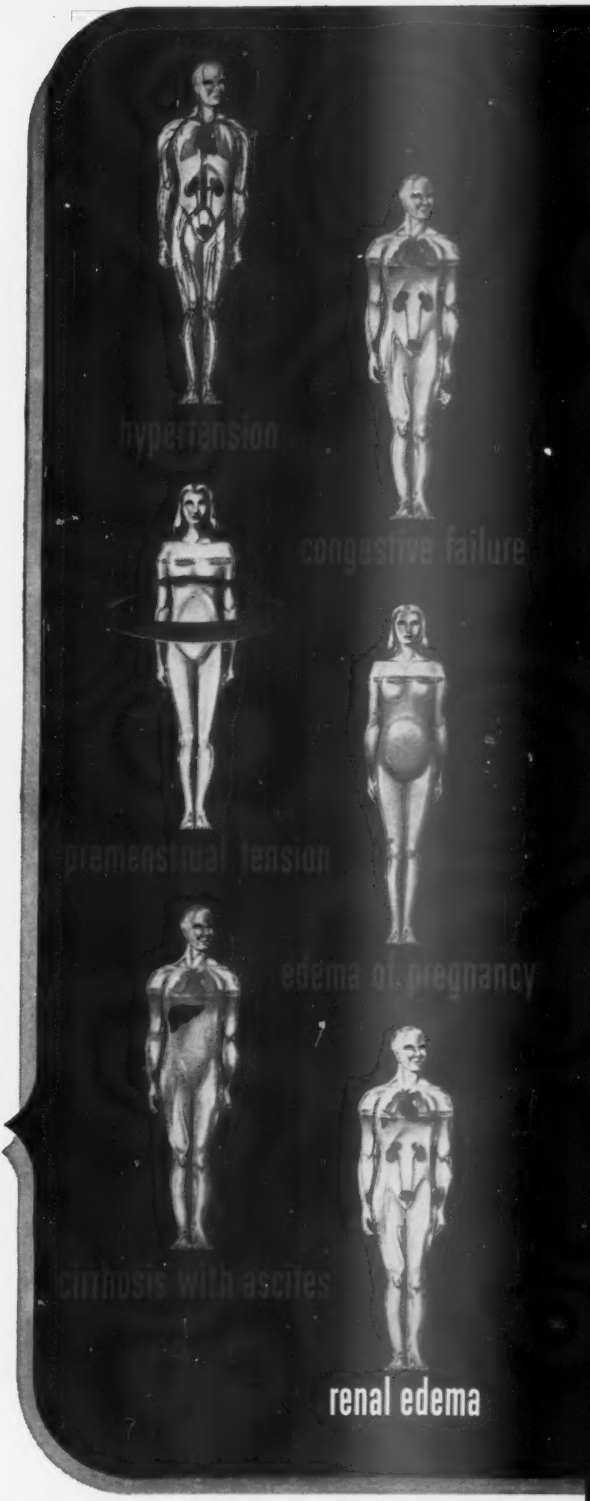

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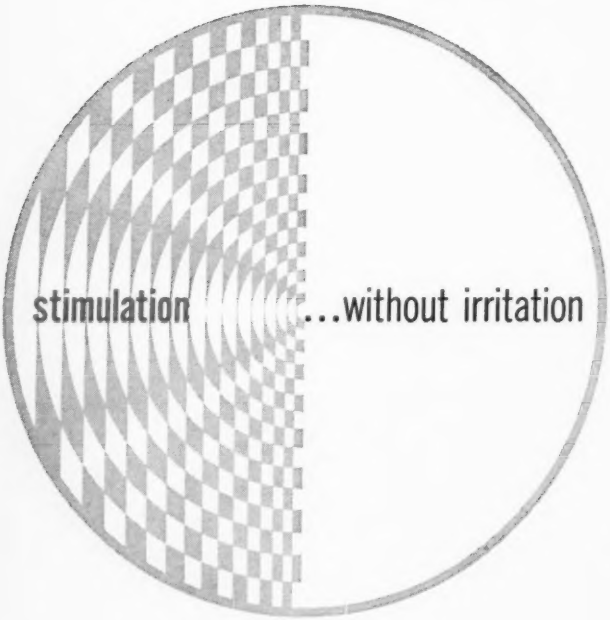

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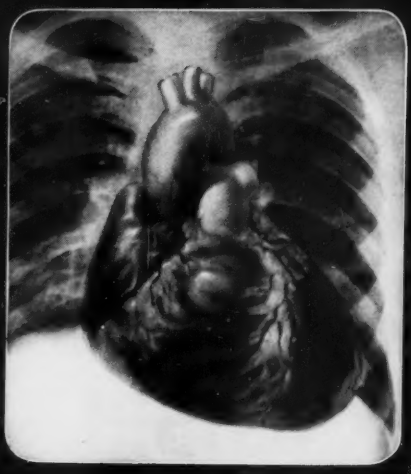

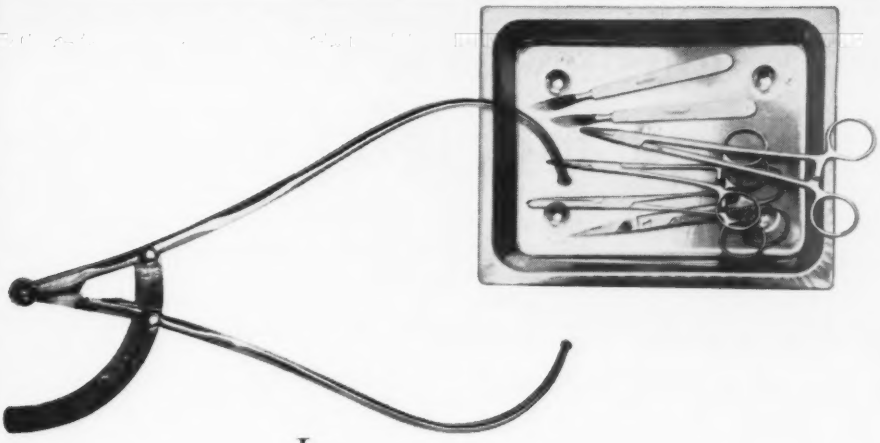

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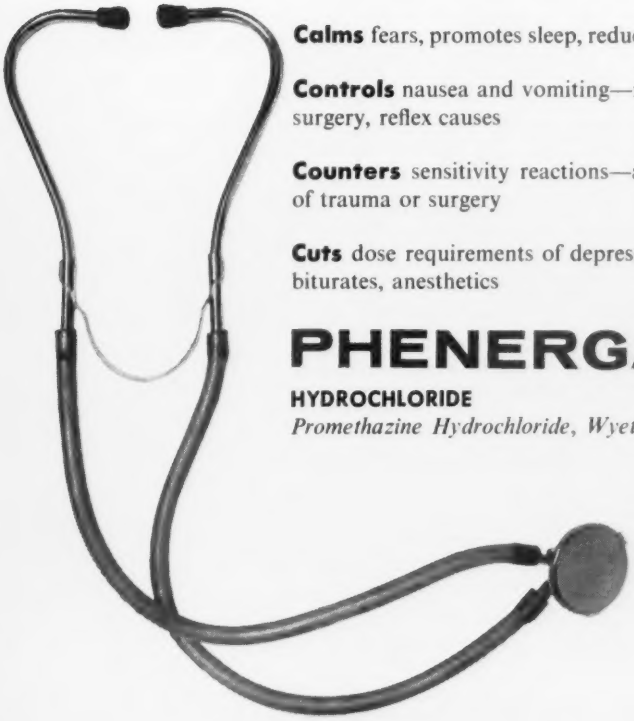

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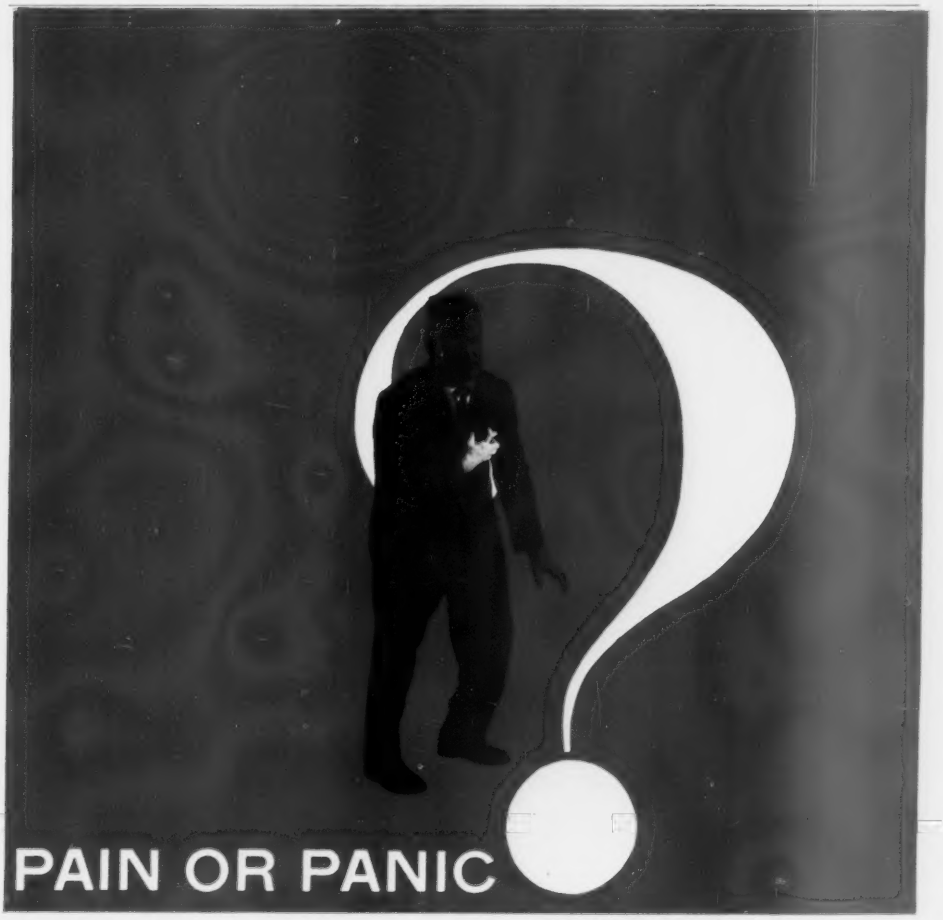
INDEX TO ADVERTISERS

JANUARY, 1960

Abbott Laboratories 15, 48–49, 57, 84–85, 98, 130–131, 156
American Cancer Society, Inc. 140
A. C. P. Directory 32
A. C. P. Postgraduate Courses 149
American Heart Association, Inc. 122
American Physiological Society, The 32
Ames Company, The 64, 138
A. I. M. Are You Moving? 122
A. I. M. Wanted Back Issues 44, 74
Armour Pharmaceutical Company 55, 148
Astra Pharmaceutical Products, Inc. 127
Ayerst Laboratories 11, 80, 147
Borcherdt Company 44
Burdick Corporation, The 88
Burroughs Wellcome & Co. (U.S.A.) Inc. 132
Burton, Parsons & Company 66
Cambridge Instrument Company, Inc. 75
Ciba Pharmaceutical Products, Inc. 18, 60, 70, 79, 102–103, 123, 164
Cutter Laboratories, Inc. 142
Davies Rose & Company, Limited 150
Eaton Laboratories 20–21, 87, 89, 158
Endo Laboratories 22, 160–161
E. Fougera & Co., *Inc.* 140
Geigy Chemical Corporation 36–37, 82, 163
Harvard University Press 4
Hyland Laboratories 19
Ives-Cameron Company 111, 112–113, 114
Knoll Pharmaceutical Company 94
LaMotte Chemical Products Company 32
Lea & Febiger 4
Lederle Laboratories, Div. American Cyanamid Co. 50, 72–73, 120–121, 152–153
Thomas, Leeming & Company 2, 134
Eli Lilly & Company ..... Third Cover
Lloyd Brothers, Inc. 139
Macmillan Company, The 1
McNeil Laboratories, Inc. 81, 154
Mead Johnson & Company 14, 162
Merck Sharp & Dohme 8–9, 40–41, 65, 86, 96, 124–125, 143, 159
Wm. S. Merrell Company, The 56
Nordson Pharmaceutical Laboratories, Inc. 30
Organon, Inc. 106–107
Pfizer Laboratories, Div. Chas. Pfizer Co. Inc. ..... Insert facing 80, 141
Pitman-Moore Company 43, 108
Riker Laboratories ..... Second Cover, 78, 172
A. H. Robins Company ..... Insert facing 32, 126
Roche Laboratories, Div. Hoffmann La Roche, Inc. 16–17, 35, 101, 136–137
J. B. Roerig & Company 171
Wm. H. Rorer, Inc. 25, 133
Sanborn Company 92
Sandoz Pharmaceuticals 62–63
W. B. Saunders Company 3
Schering Corporation 71, 95, 157
G. D. Searle & Co. 97
Smith-Dorsey Company 12–13, 116–117
Smith, Kline & French Laboratories ..... Insert facing 64, 10, 51, 93, 109, 135, 165
E. R. Squibb & Sons, Div. Olin Mathieson Chemical Corp. 7, 26, 39, 52–53, 110, 118, 155
R. J. Strasenburgh Co. 27, 29, 31
Training School, The 74
Tufts University School of Medicine 44
Upjohn Company, The 54
U. S. Vitamin Corporation 90–91, 144–145
Wallace Laboratories 23, 46, 61, 76–77, 99, 105, 122, 129, 168–169
Walker Laboratories, Inc. 28
Wampole Laboratories 104
Warner-Chilcott Laboratories 5, 47, 49, 119
Warren-Teed Products, Inc. 146
William A. Webster Co., The 74
White Laboratories, Inc. 67, 68–69, 166
Winthrop Laboratories, Inc. 42
Woodward Medical Personnel Bureau 140
Wyeth Laboratories 6, 24, 34, 58–59, 83, 100, 115, 128, 151, 167
Wynn Pharmacal Corporation 38



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